SYSTEM AND METHOD

FOR THE POOLING OF STERILE PRODUCT

by

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[3]Not only so, but we also rejoice in our sufferings, because we know that suffering produces perseverance; [4]perseverance, character; and character, hope *Romans 5:3-4 (NIV)*

July 19, 2007

ABSTRACT

FINAL PROGAM OF WORK

SYSTEM AND METHOD FOR THE POOLING OF STERILE PRODUCT

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This dissertation defines an automated system and method for removing the tops from individual sealed bottles and pooling the small volumes of liquid contained in each bottle together in a collection container while maintaining the sterility of the product. This research further applied system development and process improvement methodology.

More particularly, this research solved a previously unsolved problem through the unique research and development, and application of ultrasonic technology, to mitigate both product and personnel risk, and provide process improvement, as associated with the aseptic process for the pooling of sterile product.

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CHAPTER 1

INTRODUCTION

1.1 Problem Statement

The objective of this research is to develop a system and method for the transfer of sterile solution.

This research solves a currently unsolved problem through unique research and development, and application of technology, to mitigate both product and personnel risk, and provide process improvement for the aseptic process for the pooling of sterile product.

1.2 Background

This research addresses the aseptic process related to the sterile transfer, or pooling of product, in support of clinical trials to meet regulatory compliance. This process is commonly completed within the Research and Development (R&D) function of a pharmaceutical organization but may also be within a manufacturing operation.

To gain understanding, the following offers a brief summary of terminology and processing approaches typical in the processing of sterile drugs for the pharmaceutical industry, an industry that is regulated around the world to protect users and assure drug safety and efficacy.

Finally, within this section, is a discussion of the application of this process in support of clinical studies, a regulatory requirement, and market studies.

1.3 Definitions

Following are a couple of core definitions, from Merriam-Webster's Medical Dictionary (©2002 Merriam-Webster, Inc.):

Sterile - 1: failing to produce or incapable of producing offspring, 2: free from living organisms and especially microorganisms — sterilely/ adverb — sterility/ noun plural -ties

Aseptic - 1:preventing infection <aseptic techniques> 2: free or freed from pathogenic microorganisms <an aseptic operating room> —aseptically/ adverb

1.4 Pharmaceutical Processing

Common to the pharmaceutical industry are two basic approaches related to the processing and packaging of sterile drug products', Terminal Sterilization, and Aseptic Processing.

Terminal sterilization typically involves liquid filling and sealing product containers under tightly controlled, high quality, environmental conditions. Conditions include monitoring of temperature, relative humidity, uni-directional air flow, positive pressure to surrounding areas, non-viable particulate counts and viable sampling during processing. Products are filled and sealed in this type of environment to minimize the microbial and particulate content of the in-process product and to help ensure that the subsequent sterilization process is successful. In most cases, the product, container, and

closure have low bioburden, but they are not sterile. The product in its final container is then subjected to a sterilization process such as heat or irradiation.

In an aseptic process, the drug product, container, and closure are first subjected to sterilization methods separately, as appropriate, and then brought together for final assembly. Because there is no process to sterilize the product in its final container, it is critical that containers be filled and sealed in an extremely high-quality environment.

Aseptic processing involves far more variables, and therefore risk, than terminal sterilization. Prior to aseptic assembly into a final product, the individual parts of the final product are generally subjected to a dedicated sterilization process via dry heat, moist heat, irradiation or sterile filtration. Each of these manufacturing processes requires verification, validation and control as these components arrive from a variety of sources and transit methods to the final point of assembly.

Any failure in manual or mechanical manipulation of sterilized drugs, components, containers, or closures prior to or during aseptic assembly could introduce an error that ultimately could lead to the distribution of a contaminated product, which can ultimately pose a life-threatening health risk to users.

1.5 Clinical Trials

The ideas for clinical trials typically come from researchers. After researchers test new therapies in the laboratory and in animal studies, the experimental treatments with the most promising results are advanced into what are termed clinical trials. During

clinical trials, more and more information is gained about an experimental treatment, its risks and how well it may, or may not, work.

The most commonly performed clinical trials evaluate new drugs, medical devices, biologics, or other interventions to patients in scientifically controlled settings, and are required for regulatory (United States Food and Drug Administration) approval of new therapies. Trials may be designed to assess the safety and efficacy of an experimental therapy, to assess whether the new intervention is better than standard therapy, or to compare the efficacy of two standard or marketed products. The trial objectives and design are documented in a Clinical trial protocol.

Trials occur in a variety of locations, such as hospitals, universities, doctors' offices, or community clinics. To be ethical, they must involve the full and informed consent of participating human subjects. They are closely supervised by appropriate regulatory and scientific authorities. All interventional studies must be approved by an ethics committee (e.g. in the USA, this body is the Institutional Review Board) before permission is granted to execute the trial.

Clinical trials may be "sponsored" by physicians and designed to test simple questions. Other clinical trials involve large numbers of participants followed over long periods of time, and the trial sponsor is more likely to be a medical institution, foundation, volunteer group, or pharmaceutical company, in addition sponsors may come from academia or federal agencies such as the National Institutes of Health (NIH), the Department of Defense (DOD), and the Department of Veteran's Affairs (VA).

While the term clinical trials is commonly associated with large studies, many clinical trials are small. The number of patients enrolled in the study has a large bearing on the ability of the trial results to reliably detect an effect of a treatment. In clinical trials, the investigators manipulate the administration of a new intervention and quantify the effect of that manipulation.

There exist different types of clinical trials. Treatment trials test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy. Prevention trials look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes. Diagnostic trials are conducted to find better tests or procedures for diagnosing a particular disease or condition. Screening trials test the best way to detect certain diseases or health conditions. Quality of Life trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.

Clinical trials are conducted in multiple phases but before even these begin, pharmaceutical companies conduct extensive pre-clinical studies involving areas like formulation, process development and toxicity.

Pharmaceutical clinical trials are commonly classified into four phases, and the drug-development process will normally proceed through all four stages over many years. If the drug successfully passes through the first three phases it will usually be successfully approved for market and used in the general population.

The trials at each phase have a different purpose and answer different questions: Phase I trials are the first stage of testing in human subjects. Researchers test an experimental drug or treatment in a small group of healthy people (typically numbering 20-80) to evaluate its safety, determine a safe dosage range, evaluate user tolerability and identify any side effects. These trials are almost always managed in a clinic where the subject can be closely observed by full-time medical staff. Phase I trials normally include dose-ranging studies and most often include healthy volunteers, however there are some circumstances when patients are used, such as those with diseases that have few, if any, other treatment choices.

There are two more specific kinds of Phase I trials - SAD studies, and MAD studies.

SAD - Single Ascending Dose studies are those in which groups of three or six patients are given a small dose of the drug and observed for a specific period of time. If they do not exhibit any adverse side effects, a new group of patients is then given a higher dose. This is continued until intolerable side effects start showing up, at which point the drug is said to have reached the Maximum tolerated dose (MTD).

MAD - Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics/pharmacodynamics of the drug. It is often summarily stated that pharmacodynamics is the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug. In these studies, a group of patients receives a low dose of the drug and the dose is subsequently escalated upto a

predetermined level. Samples are collected or tests completed at various time points and analyzed to understand how the drug is processed within the body.

Once the initial safety of the therapy has been confirmed in Phase I trials, Phase II trials are performed on larger groups (100-300) and are designed to assess efficacy of the therapy and to further evaluate its safety in a larger group of patients. The development process for a new drug commonly fails during Phase II trials due to the discovery of poor efficacy or toxic effects.

Phase III studies are large double-blind randomized controlled trials on large patient groups (1000-3000 or more). This means that each study subject is randomly assigned to receive one of the treatments, which might be the placebo. Neither the subjects nor scientists (double-blind) involved in the study know which study treatment is being administered to any given subject; and, in particular, none of those involved in the study know which subjects are being administered a placebo.

Phase III studies are conducted to confirm effectiveness, monitor any side effects, compare with commonly used treatments, and to collect information that will allow the experimental drug or treatment to be used safely. They are intended to be the definitive assessment of the efficacy of the new therapy, especially in comparison with currently available alternatives. Phase III trials are the most expensive, time-consuming and difficult trials to design and run; especially in therapies for chronic conditions. Once a drug has proven satisfactory over Phase III trials, the trial results are usually combined into a large document containing a comprehensive description of the methods

and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to various regulatory authorities in different countries, such as the Therapeutic Goods Administration (TGA) in Australia, the European Medicines Agency (EMEA) or the Food and Drug Administration (FDA) in the United States for final marketing approval.

Phase IV trials involve the long term, post-market-launch, safety surveillance and ongoing technical support of a drug. Post-marketing studies delineate additional information including the drug's risks, benefits, and optimal use. Post-launch safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and timescale than was possible during the initial clinical trials. Phase IV studies may be mandated by regulatory authorities or may be undertaken by the sponsor for competitive or other reasons.

Most human use of investigational new drugs first takes place in controlled clinical trials conducted to assess safety and efficacy of new drugs. Data from the trials serve as the basis for the drug marketing application. FDA regulations enable manufacturers of investigational new drugs to provide for "expanded access" use of the drug. For example, a treatment IND (Investigational New Drug application) or treatment protocol is a relatively unrestricted study.

1.6 Market Studies

The ideas for market studies typically originate from the sales and marketing functions of an organization. These functions seek a competitive advantage in the market place by claiming their product is better than others. Claims can be made verbally or through advertising but in either case must be supported through documented experimentation.

In market studies, the products are those already released and commercially available.

The focus of this research, these products are transferred from their commercial packaging (i.e. bottle or droptainer) and collected, or pooled, into a bulk container. The container of pooled sterile product is later re-packaged into an identical container which matches that of the subject product. Each identical container is uniquely coded so as to individually track for comparison of patient experience and response to use.

This results in a "blind study" or collection of various products that have no visual difference in appearance to a user, the only difference is in the contained product under study and comparison.

Studies are conducted within the same clinical trials format so data gathered may be used for any future product claims or in defense of litigation.

1.7 Current Process

Three to four skilled and educated scientists within a small scale, research and development, aseptic processing environment, routinely manually execute the current

process. This product pooling process collects solution from previously packaged, pharmaceutical, sterile products and pools it into a collection container. Upon process completion this collection container is sealed and later used in the re-packaging of the pooled product. The repackaged product is then used to support clinical trials and market studies or competitive product market comparisons.

Starting product varies in bottle size, shape and plastic material. Figure 1.1. shows a representative sample of round and oval bottles typically processed.

Figure 1.1 – Sample of Bottles Processed

To assist in providing an "as is" understanding of the current process, Figure 1.2 shows the relationships of the Inputs, Controls, Outputs and Mechanisms to the manual product pooling process.

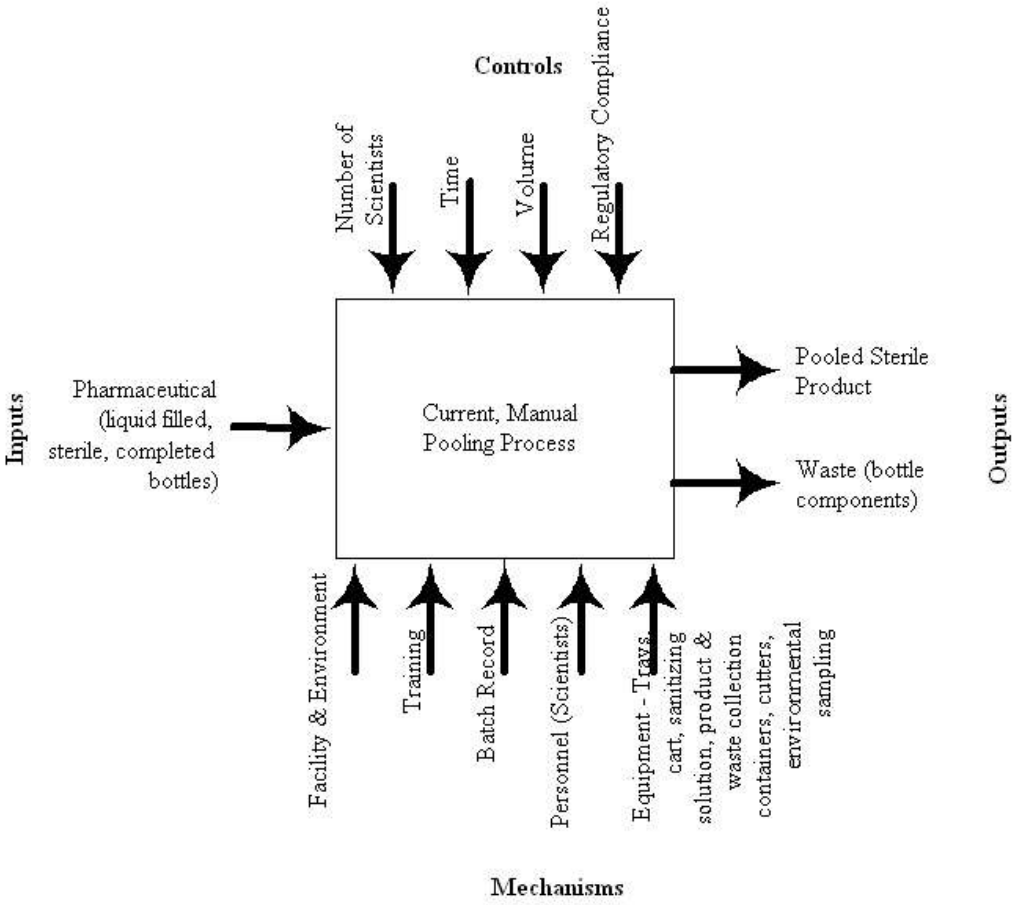
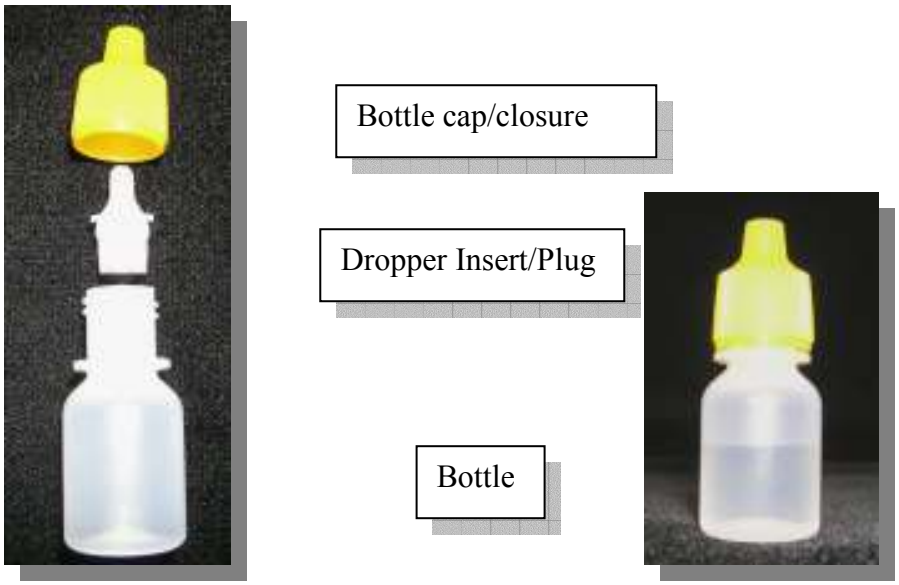


Figure 1.2 – Current Process

Process Sequence/Description:

Completed plastic bottles, filled with an identical sterile pharmaceutical product, are purchased, or otherwise obtained. Definition of a "complete bottle" (reference Figure 1.3) is a plastic bottle/droptainer, filled with various volumes of sterile solution, in some cases with a dropper insert for dispensing of product, and top plastic cap closure for sealing the solution within the bottle.



Components Assembly, Liquid Filled

Figure 1.3 – Typical Bottle, Components & Assembly

Secondary packaging, removed prior to processing, may be a label on the bottle and a tamper evidence seal around the bottle cap and bottle neck. The injection molded, plastic, bottles vary in shape, dimension, fill volume and material of construction.

Bottles are prepared in a non-controlled environment by first removing any outside labeling or tamper evidence seals.

Within the same environment, bottles are next manually staged within trays (reference Figure 1.4), typically located on a stainless steel cart, in the upright position with open spacing around each such that no bottle is touching another.

Figure 1.4– Bottles Staged for Processing

Moving this cart to a controlled environment, all bottle surfaces are sprayed thoroughly with a liquid sanitizing solution to reduce surface bioburden prior to processing.

Separately, needed tools, a collection funnel and a product bulk collection container are terminally sterilized, moved into higher level controlled environment (clean room) and readied for the collection of solution.

The cart, with vial trays, is then transferred into a higher level of controlled area (clean room) by trained and fully gowned (no exposed skin) scientists.

Scientists pre-stage the trays on a stainless steel table located under unidirectional air flow in the clean room in preparation for start of processing.

Processing begins with fully sterile gowned (no exposed skin) scientists sitting around a table, reference Figure 1.5. Bottles are each individually processed by typically four scientists.

Figure 1.5 – Manual Product Pooling, In Process

Each scientist manually picks a single bottle from the tray, grips with one hand and rotates the bottle top counterclockwise with the other hand to remove the top closure. Next the top insert (for droptainers) is manually pulled from the bottle using pre-sterilized tools. An alternative for some product containers is gripping the bottle with one hand and physically cutting the top off of the bottle with the other using pre-sterilized cutters.

No matter the means utilized the bottle tops are then disposed of into waste containers.

The exposed bottle bottom, containing sterile liquid, is then raised and extended by the scientist over a pre-sterilized glass funnel at which time the bottle is rotated emptying its contents into the collection container. Only one bottle at a time is allowed over the glass funnel area.

Empty bottle is lowered and manually disposed of into a waste collection container.

The process is repeated until all vials are processed. Batch quantity is typically 1500 to 2000.

Upon completion, waste is collected and removed from the area and the product collection container is sealed for future re-packaging.

1.8 Need / Significance of Research

Product sterility is the key parameter in this process. Consideration of labor and cycle time is important in order to minimize cost and risk of contamination of the product, or risk to personnel.

The manual process outlined above has resulted in loss of product due to contamination from two sources. Each occurrence has required product disposal amounting to a financial loss of well over $100,000 per occurrence not accounting for the unknown losses in studies not continued or initiated. This first cause of product contamination is from carry over of sanitization solution into the collected product. This carryover has been traced to both bottle surfaces and to the gloved hands of scientists. Second cause of contamination is a direct result of this manual intensive process combined with required movements and prolonged cycle time. Scientists become tired and in pain resulting in processing mishaps. Additional contribution may be excessive number of scientists working in a limited aseptic processing area.

This process is performed manually throughout the pharmaceutical industry. Research of this process changes the way the industry completes this process, reduces risk of product loss, offers a competitive advantage and eliminates the risk of repetitive motion injury to personnel.

This research answers the question of what technology, system and method, can be developed to maintain product sterility and minimize risk to employees. Additionally, what minimum cycle time can be achieved and what are the

corresponding labor levels. This minimum processing time will result in less exposure and risk to the product and reduction of personnel complaints in terms of repetitive motion discomfort.

In summary, problems with the current product pooling system process are primarily; (1) product contamination, (2) manual operation, which results in excessive time taken to complete the process and also leads to potential personnel injury, and (3) excessive cost of processing.

Product contamination occurs as result of the required surface sanitization of the starting product filled bottles. This surface sanitization product can be transferred to the pooled product by means of hand contact with product transfer components or by scientists whom frequently report discomfort and fatigue after processing. Past failures have resulted when a bottle in process is inadvertently dropped into the product collection funnel contaminating the collected solution. Another occurrence was product poured from a bottle in process over a second scientist's hand while more than one scientist had been unloading a bottle at one time into the product collection container. The result in each case is all solution is discarded at a very high financial loss. Also, when this occurs, processing has ended for the day and a "processing day" is lost.

Secondly, the process has taken too long, which adds to the fatigue scientists experience during processing. Scientists exit this process reporting fatigue, aching hands, wrists and shoulders.

Finally, there is a excessive cost of processing that is associated with the final collected product in terms of time and personnel required. This cost is transferred to the requesting department or marketing group at actual. Any reduction in cost is a net gain or benefit to the organization.

1.9 Dissertation Objective

The objective of this research is to develop a system and method for the pooling of sterile solution.

This research solves a currently unsolved problem through the unique research and development, and application of technology, to mitigate both product and personnel risk, and reduce cost of operations, as associated with the aseptic process for the pooling of sterile product.

This research defines an automated system and method for removing the tops from individual sealed bottles and pooling the small volumes of liquid contained in each bottle together in a collection container while maintaining the sterility of the product liquid. This research further applies system development and process improvement methodology.

1.10 Research Approach

In order to accomplish the research, tasks were developed and defined, and further outlined, within a "Research Plan", reference Table 3.3.

The end product of this research is a system and method that changes the way in which industry meets the challenge for the sterile transfer, or pooling, of solution. This

system may be used to pool solution while maintaining sterility of the product to support a business's clinical and marketing studies. The research additionally provides a method which reduces processing cost, resources and eliminates the risk of injury to operating personnel.

1.11 Dissertation Outline

Chapter 1 of the dissertation develops the business need for this research. Background is offered in pharmaceutical processing and definitions. The research need is defined through definition of clinical trials and market studies in addition to deficiencies of the current process. Chapter 1 states the objective of the research and the tasks required to successfully achieve the objective.

Chapter 2 of the dissertation summarizes current literature related to this research. Due to the scope of this research intellectual property (IP) is also summarized to demonstrate this research is truly unique.

Chapter 3 of the dissertation restates the objective and outlines the research methodology and research plan. Limitations of the research are discussed as well as the contribution to knowledge.

Chapter 4 of the dissertation presents the results of the executed research plan. An in depth discussion of tasks with related results are presented. In addition, an overall conclusion is outlined.

Appendices to the dissertation offer supporting documentation to the research effort, detailed information regarding vendors, patents and trademarks relative to the

research, system bid specification and raw data from the research. Supporting software information is provided. References and biographical information complete the dissertation.

CHAPTER 2

LITERATURE REVIEW

The objective of this research is to develop a system and method for the transfer of sterile solution.

2.1 Introduction

The literature review has been expanded to include prior use of ultrasonics in the cutting of plastics and research in the area of ultrasonic cutting in general as no results were found for ultrasonic use in the cutting of plastics within a aseptic environment.

2.2 Ultrasonics – The Beginning

The earliest development of ultrasonics during the late-1910's for military underwater sound transmission use is discussed by author Jennet Conant (Tuxedo Park: A Wall Street Tycoon and the Secret Palace of Science That Changed the Course of World War II, Simon & Schuster, New York (2002)).

The author covers the life of Alfred Lee Loomis**,** a Wall Street tycoon, a famous scientist, a lawyer and a legend in the history of the United States. Born of upper-middle-class parents, Loomis was a brilliant mathematics major and inventor at Yale University. After attending Harvard Law School, he joined a prominent Wall Street law firm.

During the first World War, he used his undergraduate training in mathematics and science, along with his detailed knowledge of European field artillery - an interest developed in college - to secure the assignments he wanted: first to the old Army proving ground at Sandy Hook, New Jersey, and later to the new Aberdeen Proving Ground in Maryland, which opened for business in January 1918.

The modern ultrasonics era arose from Professor Paul Langevin's 1917 invention of the quartz sandwich transducer for underwater sound transmission in submarine detection. Loomis renewed the wartime acquaintance with Professor Robert Wood and offered to collaborate and underwrite any joint research ventures.

In 1926, Wood told Loomis of Langevin's experiments and suggested the subject offered a wide field for research in physics, chemistry, and biology. It was this group that had allegedly introduced ultrasound to chemistry in 1927.

2.3. Ultrasonic Cutting

The first useful description of the technique of ultrasonic machining was given in the 1940's by Lewis Balamuth (1945). By 1953-1954, the first ultrasonic machine tools (mostly on the basis of drilling and milling machines) had been built (Rozenberg et al., 1964). By 1960's, ultrasonic machine tools of various types and sizes for a variety of purposes had been seen and some models had begun to come into regular production.

The focus and principles of using ultrasonic’s for cutting brittle materials was first developed and published by L.D. Rozenberg, V.F. Kazantsev, L.O. Makarov and D.F. Yakhimovich (Ultrasonic Cutting, New York, Consultants Bureau, 1964) and

Rozenberg and Woods (Physical Principles of Ultrasonic Technology (1973), Physical Principles of Ultrasonic Technology, Vol. 1 (1973) and Vol. 2 (1973).

These authors presented, originally in Russian, translated to English, a comprehensive summary of work to date and elementary theories of ultrasonic's as used in machining of brittle materials. They further offered theory and design of the acoustic portions of machining tools and those used for surface impact grinding.

The authors focused on the need for methods to work "unworkable materials" such as germanium, silicon, ferrites, ceramics, glass and quartz on account of great brittleness. They offered that first papers appeared in 1951-1952 with the first ultrasonic tools made in 1953-1954 mostly for drilling and milling. Principal producers of equipment in capitalist countries were Sheffield and Ratheon in the USA, Mullard and Kerry in Great Britain, Lehfeldt in Germany and certain firms in France and Itlay.

The tool oscillates at high frequency (typically >20 kHz) and is fed into a workpiece by a constant force. An abrasive slurry comprising water and small abrasive particles is supplied between the tool tip and the workpiece. Material removal occurs when the abrasive particles, suspended in the slurry between the tool and workpiece, impact the workpiece due to the downstroke of the vibrating tool.

One of the major differences between ultrasonic machining and rotary ultrasonic machining is that the former uses a soft tool (such as stainless steel, brass, and mild steel) and a slurry loaded with hard abrasive particles while in rotary ultrasonic machining the hard abrasive particles (diamond) are bonded on the tools. Another major

difference lies in that the rotary ultrasonic machining tool rotates and vibrates simultaneously while the ultrasonic machining tool only vibrates.

Up to early 1960's, some three to four hundred papers had been published covering the various aspects of ultrasonic machining. Much of this material was brought together by two monographs: Ultrasonic Machining of Intractable Materials by Markov (1966) and Ultrasonic Cutting by Rozenberg et al. (1964), both originally published in Russian and translated into English afterward.

However, in ultrasonic machining, the slurry has to be fed to and removed from the gap between the tool and the workpiece. Because of this fact, there are some disadvantages of this method: (1) material removal rate slows down considerably and even stops as penetration depth increases; (2) the slurry may wear the wall of the machined hole as it passes back towards the surface, which limits the accuracy, particularly for small holes; and (3) the abrasive slurry also "machines" the tool itself, thus causing considerable tool wear, which in turn makes it very difficult to hold close tolerances.

Rotary ultrasonic machining was invented by Legge (1964). In the first rotary ultrasonic machining device, the slurry was abandoned and a vibrating diamond-impregnated tool was used against a rotating workpiece. Because the workpieces were held in a rotating four-jaw chuck, with this device only circular holes could be machined and only comparatively small workpieces could be drilled.

Further improvements led to the development of a machine comprising a rotating ultrasonic transducer. The rotating transducer head made it possible to precisely machine stationary workpieces to close tolerances. With different shaped tools, the range of operations could be extended to end milling, tee slotting, dovetail cutting, screw threading and internal and external grinding (Anonymous, 1966).

The literature on rotary ultrasonic machining in the 60's and 70's can be classified into two groups: (1) the articles devoted to explaining the principle of rotary ultrasonic machining and describing the equipment and diamond tools and (2) the papers reporting the experimental investigations on the relations between the process parameters (e.g. vibration amplitude, static pressure, rotational speed and grit size, etc.) and the process performance such as tool wear and surface finish.

For a long time, rotary ultrasonic machining was viewed merely as an process improvement. In principle, however, rotary ultrasonic machining is a hybrid process which utilizes the fixed-abrasive tool used in diamond grinding and the ultrasonic vibrations associated with ultrasonic machining.

The focus of ultrasonic technology further progressed to applications of healthcare (Cancer Clinical Trials: Experimental Treatments and How They Can Help You, R Finn (1999)), plastics assembly (Guide to Ultrasonics Plastics Assembly, Dukane Corporsation (1995)) and non-destructive testing (R. W. Cribbs, Non-Destructive Testing - Volume 2, Issue 4 , November 1969, Pages 248-250) in measuring refractive index and thickness and for detecting flaws in dielectric materials.

Authors, researchers at Russian Academy of Sciences and the Loughborough University Department of Mechanical Engineering, respectively, considered the superimposing of ultrasonic's over machining process (Ultrasonic cutting as a nonlinear (vibro-impact) process, K. Astashev and V. I. Babitsky, Ultrasonics - Volume 36, Issues 1-5 , February 1998, Pages 89-96). The accumulated experimental results are explained theoretically in the framework of rheological models. It is confirmed that under the influence of high frequency vibration, the phenomenological transformation of elasto-plasticity into visco-plasticity and fluidization of dry friction occurs. The dynamic characteristics of transformed machining processes are obtained. They include the dependence of reduced cutting forces on the material and vibration parameters. It is shown that excitation of the vibro-impact mode of tool-work piece interaction is the most effective way of using ultrasonic influence on dynamical characteristics of machining. The dynamics of an ultrasonic cutting machine under technological load is investigated. The nonlinear amplitude response of the vibrating tool in the process of cutting is obtained. The theoretical results are confirmed by experiments. The method of stabilization of resonant ultrasonic excitation is described. The advantages of ultrasonic cutting and possible ways of using it are also discussed.

Complete literature review with abstracts, as applicable and as not previously mentioned, are listed in Table 2.1.

Table 2.1 – Annotated Bibliography

Mechanical Impedance Transformers in Relation to Ultrasonic Machining Lewis Balamuth Research and Development Division, Cavitron Equipment Corporation, Long Island City, New York 1954 Acoustical Society of America Abstract: Ultrasonic machining of hard materials, such as cemented carbides, steel, sapphire, etc., requires the use of an acoustical transmission line. This line generally consists of a specially shaped solid body designed so as to convey the ultrasonic vibrations of the transducer to the tool which operates on the work piece. This paper deals with a general type of mechanical impedance transformer suitable for the above-stated purposes. The theory has been cast in such form that the design of such lines may be made from universal equations and graphs. Because such equations appear in terms of ratios, one set of curves applies to all materials and to any desired frequency range. Several cases will be treated in detail so as to make the method employed clear. In addition examples will be given of actual transformers with an account of their performance in practical cases.

Table 2.1 – continued

As is the case generally with transformers, the systems described in this paper have applications in many cases where transformation of the ultrasonic vibration amplitude is desired in going from the source generator to the output end of the system.
Ultrasonic Cutting Author: L. D. Rozenberg. V.F. Kazantsev, L.O. Makarov, and D.F. Yakhimovich Authorized translation from the Russian by J.E.S. Bradley, B.Sc.,Ph.D. Publisher: New York, Consultants Bureau, 1964 ISBN: 0306106906 OCLC: 2017201 Abstract: This book presents a logical development of the subject. Starting in the first chapter with basic information covering definitions, concepts, and equations needed to understand the high-frequency energy transformations encountered in ultrasonic impact grinding. The second chapter presents original work initiated to elucidate the nature of ultrasonic grinding. It also includes the work of others which are covered in the text in the appended bibliography. The remaining three chapters contain the practical, engineering heart of the book.

Table 2.1 – continued

They present in order the theory and design of the acoustical section of an ultrasonic machine tool, the design and description of ultrasonic machining tools, and finally the technology of ultrasonic machining.
Physical Principles of Ultrasonic Technology Author: L. D. Rozenberg, Contribution by James S. Wood Publisher: Plenum Press (1973) ISBN: 0306350424 Abstract**:** The following questions are examined: ultrasonic cutting, and surface finishing of materials; degasification of liquids; and crystallization of metals.
Physical Principles of Ultrasonic Technology, Vol. 1 Author: L. D. Rozenberg, Translated from Russian by James S. Wood Publisher: Plenum Press (1973) ISBN: 0306350416 Abstract: The first volume in ultrasonics technology, the text is a series of monographs translated from Russian. The Russian text was originally published by Nauka Press in Moscow in 1970.

Table 2.1 – continued

In Volume 1 the author offers an investigation of ultrasonic cutting mechanism for machining operations including theory of the process and the disintegration of material. Forces present and effects of machining speeds are considered. Ultrasonic welding of metals and use of ultrasonics in cleaning are also analyzed in addition to degassing of liquids (diffusion effects and mass transfer).
Physical Principles of Ultrasonic Technology, Vol. 2 Author: L. D. Rozenberg, Translated from Russian by James S. Wood Publisher: Plenum Press (1973) ISBN: 0306350424 Abstract: The second volume in ultrasonics technology, the text is a series of monographs translated from Russian. The Russian text was originally published by Nauka Press in Moscow in 1970. In Volume 2 the author considers the application of acoustic vibrations converting liquid into an aerosol state at the interface between a gaseous and a liquid medium. Acoustic energy can be delivered to the atomization zone either on the liquid side or on the gaseous side.

Table 2.1 – continued

Ordinarily, when acoustic energy is delivered through the gas, the atomization of the liquid is realized by sonic and low-frequency ultrasonic vibrations because high-frequency ultrasound is rapidly damped in propagation through gases. But if the acoustic energy is delivered through the liquid, whose damping factor is orders of magnitude smaller than in gases, atomization can be realized by sonic, low frequency ultrasonic vibrations or high frequency ultrasonic vibrations.
Guide to Ultrasonics Plastics Assembly Publisher: Dukane Corporation (1995) Dukane Part Number: 403-536 Abstract: Vendor developed guide offering the basics of ultrasonics and progressing through characteristics of plastics and ultrasonic welding compatibility. Exploration of joint and part design, and assembly techniques are reviewed. Major ultrasonic generator and system components in addition opt overall process control are offered in detail and specific to the vendors offerings. Maintenance, troubleshooting and support is also defined.

Table 2.1 – continued

Tuxedo Park: A Wall Street Tycoon and the Secret Palace of Science That Changed the Course of World War II Simon & Schuster, New York (2002) Copyright by Jennet Conant. ISBN 0-684-87287-0 0-684-87288-9 (Pbk) Abstract: The book covers the life of Alfred Lee Loomis**,** a Wall Street tycoon, a famous scientist, a lawyer and a true legend in the history of the United States. Born of upper-middle-class parents, Loomis was a brilliant mathematics major and inventor at Yale University. After attending Harvard Law School, he joined a prominent Wall Street law firm. During the first World War, he used his undergraduate training in mathematics and science, along with his detailed knowledge of European field artillery---an interest developed in college-to secure the assignments he wanted: first to the old Army proving ground at Sandy Hook, New Jersey, and later to the new Aberdeen Proving Ground in Maryland, which opened for business in January 1918.

Table 2.1 – continued

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R. W. Cribbs (1969) Non-Destructive Testing - Volume 2, Issue 4 , November 1969, Pages 248-250 The Uses of Swept Frequency Microwaves Abstract: The author, a researcher with Electro-physics Co, Folsom, California, investigated the use of a microwave frequency domain interferometer for measuring refractive index and thickness and for detecting flaws in dielectric materials. This pulse-echo technique has been used on sample thicknesses from less than 10mm to over 1m; it can resolve defects as small as 2mm in diameter or 0.025mm in thickness.

Table 2.1 – continued

Thickness measurements were found to be more accurate than with ultrasonics for most plastics. Refractive index measurements are accurate and do not require cutting the samples for insertion into a waveguide.
K. Astashev [a] and V. I. Babitsky[b] (1998) Ultrasonics - Volume 36, Issues 1-5 , February 1998, Pages 89-96 [a] Blagonravov Institute of Machine Studies, Russian Academy of Sciences, Griboedov st. 4, 101830, Moscow, Russia [b] Department of Mechanical Engineering, Loughborough University, Loughhorough, Leicestershire LE11 3TU, UK Ultrasonic cutting as a nonlinear (vibro-impact) process Abstract: The authors, researchers at Russian Academy of Sciences and the Loughborough University Department of Mechanical Engineering, respectively, with consider the superimposing of ultrasonics over machining process. The accumulated experimental results are explained theoretically in the framework of rheological models. It is confirmed that under the influence of high frequency vibration, the phenomenological transformation of elasto-plasticity into visco-plasticity and fluidization of dry friction occurs.

Table 2.1 – continued

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Masahiko Jin and Masao Murakawa (2001) Journal of Materials Processing Technology - Volume 113, Issues 1-3 , 15 June 2001, Pages 342-347 Abstract: The authors, from the Dept. of Mechanical Engineering, Nippon Institute of Technology, Japan, investigate a combination of countermeasures to prevent the chipping of the edge of a cutting tool. This chipping usually occurs when difficult-to-cut materials such as hardened steels are cut by means of a conventional ultrasonic vibration cutting (UC) method.

Table 2.1 – continued

The authors consider that the chipping is caused by a collision between the flank of a cutting tool and the machined surface of a work piece when the tool moves backwards thereby contacting the work piece. As a first countermeasure they propose a new UC device which has more rigidity and stability than the previous one that they used, even when subjected to high cutting resistance. As an additional countermeasure, in addition to using the new UC device, an attempt to is made to perform a cutting operation in which the vibrational direction of the cutting tool is inclined from the principal cutting direction by 10–30° toward the work piece. It is found from the results that the chipping of the cutting edge can be effectively prevented and a good surface finish obtained by both continuous and intermittent cutting modes when cutting hardened steels.
L. Vergara, J. Gosálbez, R. Miralles and I. Bosch (2003) Ultrasonics - Volume 42, Issues 1-9 , April 2004, Pages 813-818 Proceedings of Ultrasonics International 2003 Abstract: In this presentation the authors, from ETSI Telecomunicación, Spain, propose a new technique for estimating the center frequency of the ultrasound pulse from records of backscattering noise. We start by considering that the conventional maximum frequency method can be seen as a filtering (differentiator) of the pulse

Table 2.1 – continued

spectrum magnitude followed by a searching for the zero-crossing value. The new approach replaces the differentiator by a Hilbert transformer. They show in the paper that the proposed method has less variance than the maximum frequency method. In particular, they analyze the performance assuming that the real cepstrum method is used for extracting pulse spectrum magnitude. We give an upper bound for the variance reduction when practical criteria are applied for fitting the cepstrum cut-off frequency. The analytical work is verified by real and simulated data.
C. C. Tsao and H. Hocheng (2004) International Journal of Machine Tools and Manufacture - Volume 44, Issue 10 , August 2004, Pages 1085-1090 Abstract: Taguchi analysis of delamination associated with various drill bits in drilling of composite material - Abstract: The authors, from the Department of Automatic Engineering, Ta-Hua Institute of Technology and Department of Power Mechanical Engineering, National Tsing-Hua University, Taiwan, present a prediction and evaluation of delamination factor in use of twist drill, candle stick drill and saw drill. The approach is based on Taguchi's method and the analysis of variance (ANOVA). An ultrasonic C-Scan to examine the delamination of carbon fiber-reinforced plastic (CFRP) laminate is used in this paper. Experiments were

Table 2.1 – continued

conducted to study the delamination factor under various cutting conditions. The results indicate that the feed rate and the drill diameter are recognized to make the most significant contribution to the overall performance. The objective was to establish a correlation between feed rate, spindle speed and drill diameter with the induced delamination in a CFRP laminate. The correlation was obtained by multi-variable linear regression and compared with the experimental results.
M. Xiao, Q.M. Wang, K. Sato, S. Karube, T. Soutome and H. Xu (2006) International Journal of Machine Tools and Manufacture - Volume 46, Issue 5 , April 2006, Pages 492-499 Abstract: The effect of tool geometry on regenerative instability in ultrasonic vibration cutting – Abstract: The authors, from the School of Mechanical and Power Engineering, East China University of Science, China, and the Department of Mechanical Systems Engineering, Japan, present ultrasonic vibration cutting as a cutting process has been widely used in the precision machining of difficult-to cut materials due to an enhanced cutting stability and increased productivity. The authors' previous researches have shown that chatter vibration prediction is made possible by the suggested cutting model. This paper attempts to determine cutting

Table 2.1 – continued

parameters based on regenerative chatter prediction in order to facilitate the machining objectives of high accuracy, high efficiency and low cost in ultrasonic vibration cutting. The machinability of typical hardened steel, is investigated theoretically and experimentally. The cutting model is developed by introducing an experimental cutting database of steel. The simulation and experimental results show that the work piece material parameter has a direct influence on the occurrence of regenerative chatter. In order to achieve the chatter-suppressing dynamics in hard ultrasonic vibration cutting, a stability diagram is predicted based on the simulated work displacement for tool geometry changing. The stability diagram indicates that the regions of the chatter-suppressing dynamics expand with increasing tool rake angle and decreasing tool clearance angle. It is also found from the predictive results that regenerative chatter can be suppressed by a change of tool geometry. The determined tool geometry with the aid of the computer simulation is demonstrated through actual data of ultrasonic vibration cutting. By the use of the designed tool geometry, a good experimental result is achieved.

2.4 Intellectual Property

Intellectual property (IP) for this research is the system and method for pooling small volumes of sterile liquid utilizing ultrasonic technology to mitigate both product and personnel risk. Review of previous research has been completed specific to this system and method to demonstrate this research is truly unique.

A search and review has been completed to identify potentially competing intellectual property based on two separate criteria to: First, seek out companies producing equipment or providing services for the cutting of plastic, and next, search for effective patents and trademarks on file with the United Sates Patent and Trademark office.

Looking at Table 2.2 for section reference, each section includes a review of each identified IP that may pose a risk into the proposed innovation.

Included in the Table 2.2 for each section is a column entitled “Conclusion”. In this section “Risk = ??? “ is assigned one of three risk values; Low, High or Imminent. For this research, as in industry, there is always some level of risk there for a value of ‘None” doe not exist. For the purposes of this evaluation three levels of arbitrarily defined;

Low = No expected adverse impact from continuing with research.

High = Excepted adverse response from originator of the identified intellectual property, response is expected to be manageable or avoidable through design change and/or negotiation.

Imminent = Severe response expected from continuing. Litigation and financial loss anticipated.

2.5 Summary

The interpretive summary of the current state of knowledge is that this research, type of system and method for the pooling of sterile product, does not currently exist thus illustrating the uniqueness of the research.

The search and review of literature, companies, patents and trademarks are complete.

Table 2.2 – IP Review Summary

Search Criteria	Source Reference	IP Risk	Action	Conclusion
Vendors (companies or providers)	Polar Process, Inc. New Hamburg, Ontario, Canada	Competitors or providers, potentially with secrets not patented or otherwise published	Review of 8 potentially key providers	Risk = LOW
	Suhr Cutters, A/S Biskop, Denmark			
	Herrmann Ultrasonics Schaumburg, Illinois			
	Branson Ultrasonics Danbury, Connecticut			
	Accusonics', Inc. Darien, Illinois			
	Sonobond Ultrasonics West Chester, Pennsylvania			
	FFR Ultrasonics, LTD. Queniborough, Leicestershire, UK			
	Dukane Ultrasonics, Inc. St. Charles, Illinois			
Patents	United States Patent & Trademarks Office	Patent Infringement resulting in litigation	Review of 2 results found*	Risk = LOW
Trademark	United States Patent & Trademarks Office	Duplication resulting in litigation	Review of 24 results found*	Risk = LOW

* = reference Appendix B

CHAPTER 3

DISSERTATION PLAN

The objective of this research was to develop a system and method for the pooling, or transfer, of sterile solution.

The objective was accomplished by initially evaluating the current manual product pooling process. Next was to consider, possibly prototype, then develop unique automation and apply technology to replace the manual process.

This dissertation specifically develops a system and method for emptying small volumes of liquid from individual bottles; more particularly, the dissertation relates to an automated system and method for removing the tops from individual sealed bottles and pooling the small volumes of liquid contained in each bottle together in a collection container while maintaining the sterility of the product liquid.

Analysis was to the level required to meet the objectives set forth in the Research Plan.

3.1 Research Methodology

Engineers, with base knowledge gained in the completion of their undergraduate course work, enter the workforce with what equates to a "tool box" to draw from as career situations present themselves. The method in which tools are utilized for knowledge work and the results achieved, define success for engineers as they travel their career path.

Utilizing gained education and experience, this dissertation project researches, develops and implements a solution to the problem of manually processing sterile filled bottles and pooling sterile liquid. By considering and reviewing alternatives a single path is chosen and further defined.

Table 3.1 – Research Plan

Task	Description
1	Selection of general area of research
2	Process automation/application of technology
3	Process Selection/Baseline Data
4	Evaluation of manual sterile transfer/pooling process
5	Interview scientists
6	Video current process
7	Research
8	Start / Dream
9	Explore technology
10	Prototype
11	injection/vacuum transfer ?
12	hot wire ?
13	ultrasonic's ?
14	Automation
15	Prepare
16	Preliminary testing
17	Develop scope

Table 3.1 – continued

Task	Description
18	User Support
19	Management Support
20	Functional spec/Sequence of Operations
21	Bid Specification
22	Act
23	Capital Project/Justification
24	System Purchase
25	MOI (memorandum of invention)
26	Adjust
27	Engineering and Fabrication
28	Materials of Construction
29	Control System
30	Mechanical
31	Fabrication
32	FAT (factory acceptance testing)
33	shipment/delivery/installation
34	Test and Evaluation
35	Design/Installation
36	documentation
37	hardware inspection
38	software/firmware
39	dimensional verification
40	utility requirements (air, power)
41	materials of construction
42	power and energy data collection
43	confirmation test-sanitization solution carryover
44	confirmation test-particulate carryover
45	calibration
46	Operational
47	Software configuration/code
48	normal operations verification
49	SOP draft
50	abnormal conditions response verification
51	Performance
52	Install in aseptic/controlled environment
53	environmental (temp, RH, dP)
54	personnel

Table 3.1 – continued

Task	Description
55	static/dynamic air flow pattern
56	sanitization
57	viable/non-viable sampling
58	product sterility via media simulation
59	Close
60	Dissertation write-up
61	Defense presentation

3.2 Limitations

Boundaries of the system considered were;

- Processing is completed within a single, controlled, aseptic processing environment.
- All required support systems were in place, and operational, for personnel and staging of system needed equipment and materials.
- Equivalently motivated, skilled and trained scientists complete the process.
- Scientists were fully gowned with no exposed skin during processing.
- Starting product was sterile, identified and present in the aseptic processing environment in trays of known lot size and were available at a rate which does not in any way starve the process.
- Product solution was collected into a previously prepared and sterilized container.

- Collected final solution meets quality standards for sterility and remains in the aseptic processing environment.
- Process was considered as “Process Complete” when all available bottles are processed, waste was collected and all available sterile product was in the collection container.

3.3 Contribution to Knowledge

This research solved a currently unsolved problem by uniquely developing a system and method for the pooling, or transfer, of sterile solution.

Through research and development, to mitigate both product and personnel risk, and reduce cost of operations, this dissertation defines an automated system and method for removing the tops from sterile, individually sealed bottles and pooling the small volumes of liquid contained in each bottle together in a collection container while maintaining the sterility of the product liquid.

CHAPTER 4

RESEARCH AND DEVELOPMENT

This chapter focuses on the executed research from innovation, through development and finally into implementation summarized in Figure 4.1.

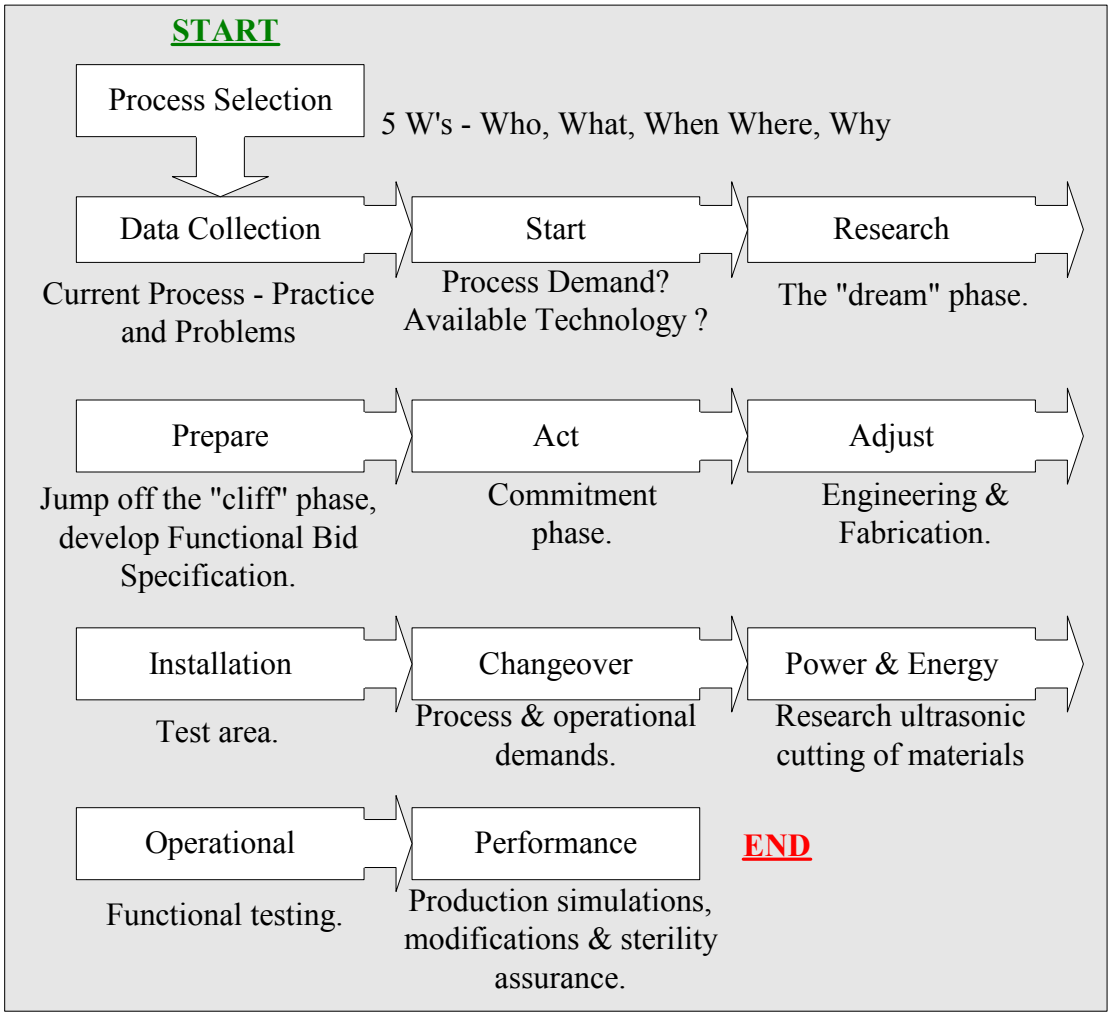


Figure 4.1 – Research and Development through Implementation

4.1 Process Selection / Innovation

Innovation may be defined as the introduction of something new, a new idea, method or device. Innovation in engineering and in business requires people effectively applying knowledge to experiment with new possibilities in order to implement concepts that create value for a organization.

This research targeted a process for innovation, which is of the "have need – find solution (pull)" type, is used to support clinical trails and market studies and is entitled "Product Pooling System or PPS".

Within a sterile processing environment, the PPS is used to collect sterile liquid solution from products, from either internal or external (e.g. competitors), into a sterile collection container. This container is then used in the re-packaging of the product. The repackaged product is used to support ongoing trials, blind studies, and competitive product market comparisons. This process is currently a very manual, labor intensive, costly process which risks both personnel and sterility of the product being pooled. Proposal is to develop an entirely new product, in the form of an automated machine, to meet this processing need. Idea for innovation was to automate the process with the design of a single machine utilizing automation and a potentially disruptive technology with the overall objectives of, assuring product sterility, eliminating personnel risk and decreasing operating cost.

Executing the Table 3.3 - Research Plan the initial step in innovation and product development was a thorough understanding of the current process. This was

accomplished in the data collection phase which involved evaluation of the current manual process.

For this research data collection began with “active listening”. As the manual process is prepared for and completed the voices of those involved can be heard. Statements like “not again” and “here comes the pain” trigger a researcher like myself to informally begin tossing around the 5 W’s – Who, What, When, Where and Why.

Who – Fully garbed (i.e. no exposed skin) Clinical scientists operating a fully manual, labor intensive, process.

What – Sterile transfer or pooling of packaged products into a sterile bulk solution container.

When – Scheduled as needed based on demand from clinical studies or on needs from marketing.

Where – Within a controlled and restricted access, pharmaceutical, sterile processing environment.

Why – Support of clinical trials, market studies and product evaluation.

Known at this point was the need for the process. The need is recognized as common practice in the pharmaceutical industry. The process of requesting and scheduling the process relative to quantity and specific product to be pooled is defined either by the study director of a given clinical trial or by marketing function. A formal request is made during routine scheduling meetings with the clinical supplies

production department. Upon review and approval the manual product pooling process is scheduled and personnel are assigned.

Data collection progressed with the objective of identifying issues and opportunities for improvement specific to the PPS. This was accomplished through more formally interviewing scientists actually performing the process. Multiple personnel were interviewed asking how the process is conducted and what manual actions are required. Responses lead to the Figure 4.2 flowchart.

Issues identified during the conversations include two main areas of risk; product and personnel. Research into the product issue included review of past process performance which highlighted two cases in the past 18 months in which post process sampling of the collected bulk solution showed positive for viable contamination. The pooled bulk solution is always sampled and tested for sterility. This is routine practice for sterility assurance prior to re-packaging or alternate use of the collected solution.

Another routine practice when a sterility failure occurs is an investigation into the root cause. This includes interview of personnel, review of all data, review of the process and the environment, and the product. The first instance resulted in the finding that multiple personnel were inverting bottles to pour liquid into the funnel at the same time which resulted in one scientist pouring product over the gloved hand of a second scientist which proceeded into the bulk container. The second incident resulted from a scientist dropping a bottle into the funnel due to cramping, tired, hands and fingers followed by a second scientist pouring product over the dropped bottle. Each incident

resulted to the total disposal of the collected solution at significant final loss in terms of product, time and resources.

The second main issue repeatedly mentioned by personnel is that of physical discomfort during and after processing. Reports of aching arms, shoulders, wrists, hands and fingers in addition to lower back pain.

The next phase of data collection involved observing and video taping the process to focus on personnel manipulations and to document processing times. Results of this phase include observation of poor aseptic processing technique and tired, uncomfortable personnel.

Initially noted is that there is too much activity and personnel in too little space. Sterile processing areas should permit space for air flow to vertically flow downward during normal operations with minimum interruption above the level of which the product is exposed. If turbulent air flow conditions exist this creates the potential to sweep less clean air, say from the floor area, back upwards and into the product contact area.

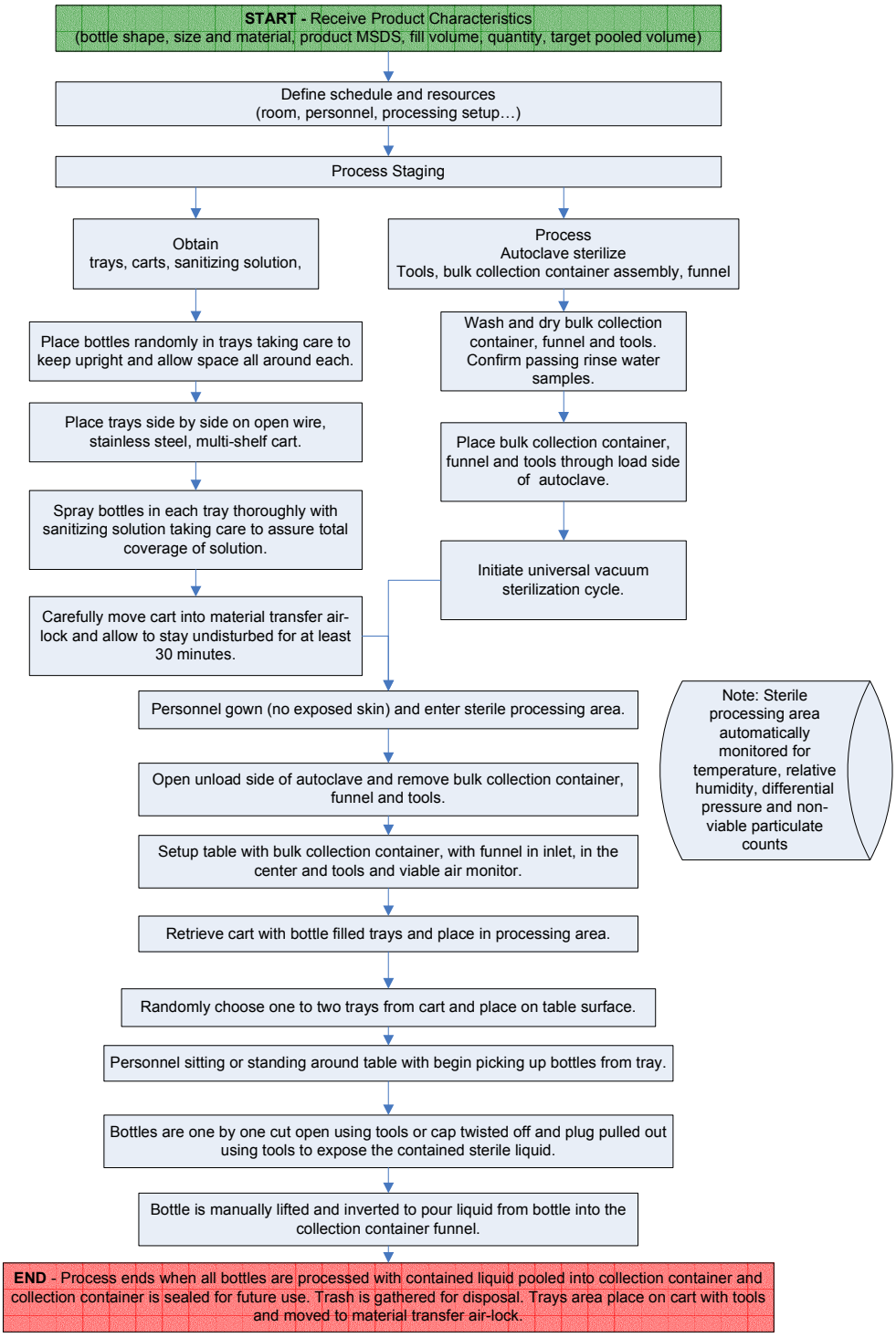


Figure 4.2 -Current Process Flow

Figure 4.3 shows a plan view of the aseptic processing area dedicated for this process. Observing the process first hand and on tape shows that too many scientists are needed to operate this manual process and too much space is occupied by the needed table and support equipment. Additionally there is too much personnel movement within this limited space to retrieve trays from the cart and stage them for processing.

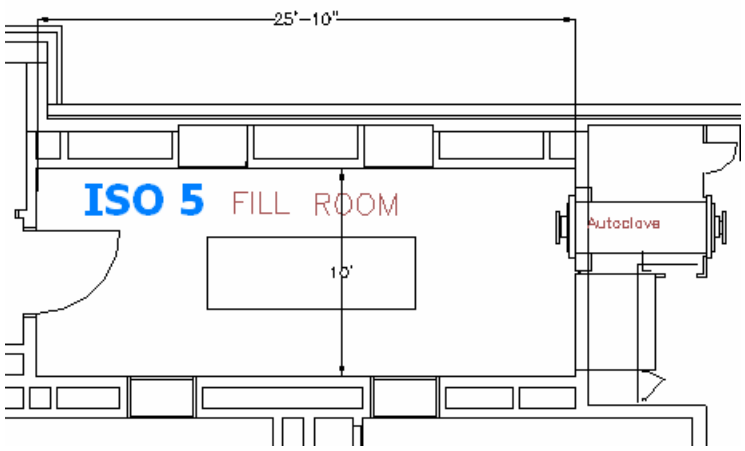


Figure 4.3 - Plan View, Aseptic Processing Room

Studying the videotape also illustrates the repetitive motion which the scientists perform during execution of the process. Figures 4.4 though 4.7 show scientist activities at various stages of the process. Of note in Figure 4.4. is the repetitive reaching from the table surface extending to the top of the product collection container funnel. This is repeated 400 to 500 times per scientist for a given process.

Figure 4.4 - Scientist Motion to Invert Bottle

The hundreds of reaching motions are in addition to the hand manipulations of either cutting or twisting to open the bottle and expose the product for pooling represented in Figure 4.5.

Figure 4.5 - Scientist Hand Manipulations

The figure below is representative of a scientist later in processing physically uncomfortable and tired from the demands of this manual process as they contemplate the remaining bottles to be processed.

Figure 4.6 - Scientist Pausing During Processing

Figure 4.7 illustrates the periodic need to change out trays. Scientists must rise from their sitting position to remove the waste tray filled with processed bottle components, the tray just processed now is moved into place and becomes the next waste tray. Scientist next walk to the cart to retrieve a new tray of bottles for processing. This is repeated by typically four scientists for 5 trays each totaling up to 2000 bottles processed.

This constant movement within the aseptic processing area further disturbs air flow within the room creating risk of contamination to the pooled product.

Figure 4.7 - Scientist Changing Out Trays to Invert Bottle

In summary, the data collection phase of this research and innovation provided documentation of the current process, review of historical performance, and identification of issues and opportunities for improvement. This was accomplished through interviewing those scientists performing the process and those serving as customers, review of past batch records and available process documentation, and videotaping the process multiple times for evaluation of movements.

With a understanding of the process including the needs of both users and customers next is to explore technology. First is to seek out commercially available, off the shelf, systems to meet the need. Querying those in industry findings were that this process is completed manually. Variations do exist in exactly which functional group may complete the process (i.e. Manufacturing, Research & Development or Marketing)

and what level of skilled personnel execute the process. The need for the process and the quality of the environment in which it is conducted does not change.

4.2 Research

With process selection completed and basic data collected sufficient to justify continuance next was the exploration of technology to define a path forward. This "dream" phase challenged myself to seek out a solution which meets the process need. Parameters like cost, operational success, resources, user acceptance, regulatory compliance and time to implementation.

Cost in this research was both known and feared. The know data is that of the cost of product lost due to failed manual processing and that of the known personnel required to complete the process. The "feared" area is the, to date, unknown cost of injury or litigation based upon injury to scientists.

Operational success speaks for itself as if whatever is developed does not perform successfully failure results and research is reversed until a successful approach is identified.

Resources are multiple in this research and include money, time, physical space, controlled environment, and testing and operating personnel.

Time to implementation for this research was a race against replacing the manual process. The faster research replaced the current manual process the greater the benefit to product sterility, personnel protection and reduced processing cost.

4.3 Start

Figure 1.2 illustrates the inputs and outputs to the process. Looking at the bottles in more detail leads to the review of the bottle material specifications.

Research began with seeking out a COTS (commercial-off-the-shelf) solution balanced against the confidentiality of not revealing the overall objectives of this process. Results of this effort were that others in the industry performing some kind of manual process and that a COTS solution was not available even though many were available, at a cost, to develop a solution.

Next, was the process of seeking out techniques that may be uniquely integrated into a process solution and simulating results. First was the prototyping of a vacuum transfer system.

It was considered that bottles could be held in a plastic or stainless steel base assembly. The sterile liquid filled bottles could then be injected or penetrated with sterile needles and the contained solution could be extracted using vacuum and pooled into a product collection container. A low cost plastic version was fabricated and testing began. Prototypes continued as different bottle holders and needles were tried, and pneumatic injectors were tested. This prototyping effort continued to the point of simulating an actual product transfer and testing the pooled solution. It was at this point that failure occurred. As mentioned previously, the bottles processed are sanitized on the exterior prior to being allowed in the sterile controlled environment for final pooling.

This exterior surface sanitization is a long standing, tested and proven, technique of reducing the bioburden of the bottle surfaces prior to sterile transfer of solution. In other words when discussion involves changing or modifying this process to accommodate downstream product pooling the direction always turns to the product pooling process.

Failure occurred when the product analyzed from this prototype process was found to included high levels of the surface sanitization components; paracetic acid and hydrogen peroxide.

Moving on to the second prototype, use of a hot wire was explored. A prototype was constructed to maintain a thin, electrically heated wire, to severe the tops from bottles. These types of cutters are typically used on foam. Parameters evaluated included:

1. Amount of heat conducted through the wire, i.e. electrical amperage flowing through wire.
2. Diameter, material and length of wire.
3. Tension on wire.
4. Support during processing to avoid electrical short of the wire support arms on the cutting bow.
5. Angle of the pull wire for cutting.

Testing provided results that the hot wire could not efficiently cut all of the bottle materials that were presented. Cutting was inefficient and left damaged cutting

surfaces. Cycle time was also slow, requiring 5 seconds or more just for cutting. Wire was not reliable at cutting 100 bottles let alone the normal process demand of 1500 or more. The search continues.

Third times a charm, right? With experience in ultrasonic sealing of package surfaces and ultrasonic generators used in cleaning processes the application of ultrasonic technology in cutting became the focus.

Informal discussion was initiated with two manufactures of the base ultrasonic generators. Information was offered to the manufacturer's limited to the type and thickness of material to be cut. One of the two manufactures, anxious for a future sale, offered and a test system. Testing was completed to demonstrate cutting efficiency, cycle time and desired generator frequency and horn type. All preliminary testing was informal, using a hand horn cutting horn and manually cutting through the neck area of bottles varying in type, size and material. This successful testing concluded the need for a 30 KHz, 1200 watt, ultrasonic system and directed research to the next level, a fully automated process system defined as the Product Pooling System or PPS.

4.4 Prepare

This what I affectionately term the "jump off the cliff" phase. The phase at which one is confident enough in a design approach to commit down a single path.

Birth of the PPS began on paper with feasibility sketches and design. Once comfortable with feasibility a more formal functional specification was developed for soliciting bids for fabrication knowing that in parallel to this process more formal and

extensive feasibility testing is going to be completed. Testing cannot be emphasized enough in research, test everything as often as possible to every extreme possible.

The Functional Bid Specification developed and issued is as included in Appendix C. Additional objectives of the this specification was to develop costs for the preparation of a funds request. This identification of "project cost" in combination with all prior data gained was used to gain approval of the initial "Go / No Go" decision.

4.5 Act

"Act" is at the point at which any needed approval was gained and that more focused research began. Funds were authorized and, based on review of solicited bids, fabrication was initiated.

4.5.1 Ultrasonic Horn Design/Fabrication

The two essential elements which set the performance characteristics of any ultrasonic application are:

1. the head assembly which comprises a converter (transducer), a mechanical amplifier (booster) and a sonotrode (horn).
2. the generator itself, enabling the head assembly to be supplied with the electrical energy necessary to activate oscillation (mechanical energy).

In regard to item 2, the generator used for this research is commercially available and is not unique to any application.

The key characteristic of the generator specified is to automatically regulate the delivery of power (watts) proportional to the load presented. Data collected during this research further quantified power delivered under load and no-load conditions.

The no-load demand was found to correspond to about 10% of the maximum power available from the generator. This minimum load serves as a “hot standby” to facilitate rapid response when the head assembly is automatically actuated and travels horizontally to the bottle target area.

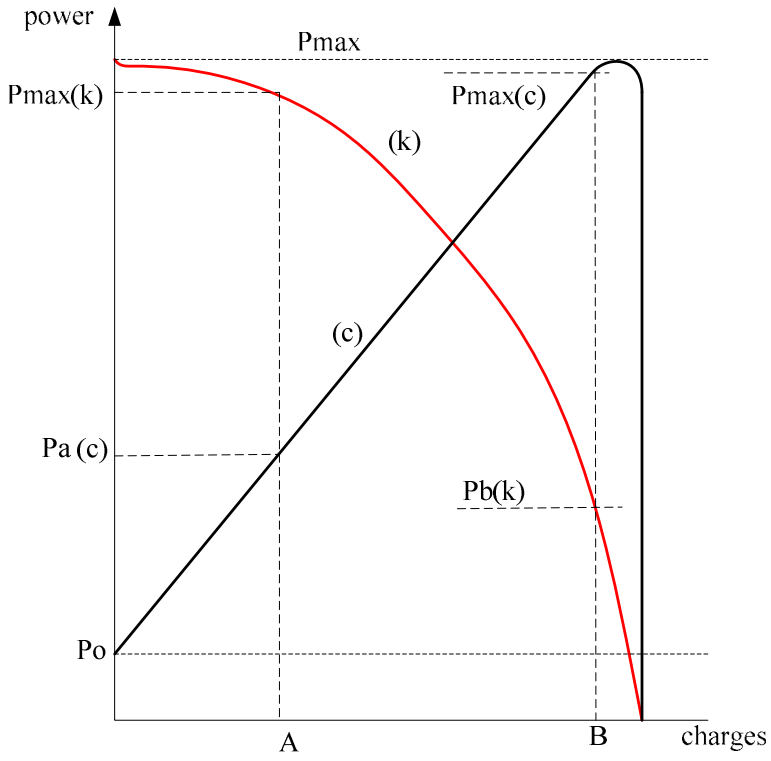


Figure 4.8 – Power Curve

Illustrated in the graph above, for load “A” and for booster “x’ horn ratio corresponding to curve “C2”, the generator delivers power “P”; this yields a power absorption factor for the target material equivalent to “Pa – Po”. “Pa” absorbed by the part represents the available power delivered by the generator corresponding to load “A”.

The proportional generator required for this research is further supported by the following two examples.

1. Low capacity (Charge A) -- A constant power generator supplies too much power for some materials when activated and not enough for others. Illustrated in the figure above, power curve (k) in relation to the power required corresponding to charge A which is automatically measured by the generator, Pa(c) but the constant delivery generator supplies maximum power, Pmax – Pa, which results in damage to the ultrasonic horn, burning of the material causing particulates and potential product contamination, and breakdown of the overloaded transducer.
2. High capacity (Charge B) - The second example, a constant power generator supplies clearly inadequate power (Pb) on curve (k) at the limit. The proportional generator used in this research supplies power at its maximum (Pmax) according to demand curve (c) thus solving the problem corresponding to charge B.

4.5.2 Head Assembly

Reverting back up to item 1 above, the head assembly comprises a converter (transducer), a mechanical amplifier (booster) and a sonotrode (horn).

The converter consists of a sandwich of mechanically pre-stressed piezoelectric ceramic discs held/sandwiched between two metal blocks. The piezoelectric discs are the motive elements of the converter. Under the effect of the electrical power produced by the generator, these ceramic discs set off the vibration of the converter.

The booster operates at the same frequency as the converter and serves to magnify the converter output vibrations to enable them to be used by the horn. For the PPS cylindrical booster, the magnification ratio is equal to the ratio between the input and output diameters:

$$R = S1/S2 = (D1)^2/(D2)^2 = 2:1$$

The horn is a machined titanium tool for the application and tuned to the same frequency as the converter and the booster. It is capable of a certain amount of additional amplification at the cutting/working end.

4.5.3 Langevin's Triplet

Recall that the modern ultrasonic's era arose from Professor Langevin's 1917 invention of the quartz sandwich transducer for underwater sound transmission in submarine detection.

Among observers of Langevin's work was Professor R. W. Wood, an American physicist from Johns Hopkins University. Already famous for his work in optics and

spectroscopy, and for his classic book "Physical Optics," he was also known as a brilliant lecturer and a writer of popular fiction and verse. With U.S. entry into WW I, Professor Wood was commissioned an Army Major and assigned to the Bureau of Inventions in Paris, where he devoted particular attention to the Langevin's work.

Another wartime meeting that proved essential to the invention of power ultrasonics occurred when Professor Wood met Alfred L. Loomis at the Aberdeen Proving Grounds. Loomis, a successful lawyer, was directing Aberdeen research as an Army Major and invented, during this time, the "Loomis chronograph" for measuring the velocities of shells. After the war, Wood pursued other areas of war research and returned to his work in optics and spectroscopy, with his interests in ultrasonic's remained dormant for several years. Loomis, following the war, entered investment banking, amassing a personal fortune during the 1920s. However, his interest returned increasingly to scientific research and, in 1924, Loomis renewed the wartime acquaintance with Wood and offered to collaborate and underwrite any joint research ventures. In 1926, Wood told Loomis of Langevin's experiments and suggested the subject offered a wide field for research in physics, chemistry, and biology.

In order to achieve delivery of high power it is desirable to use an emitter of the type developed by Professor Paul Langevin, know as "Langevin's Triplet", it consists of:

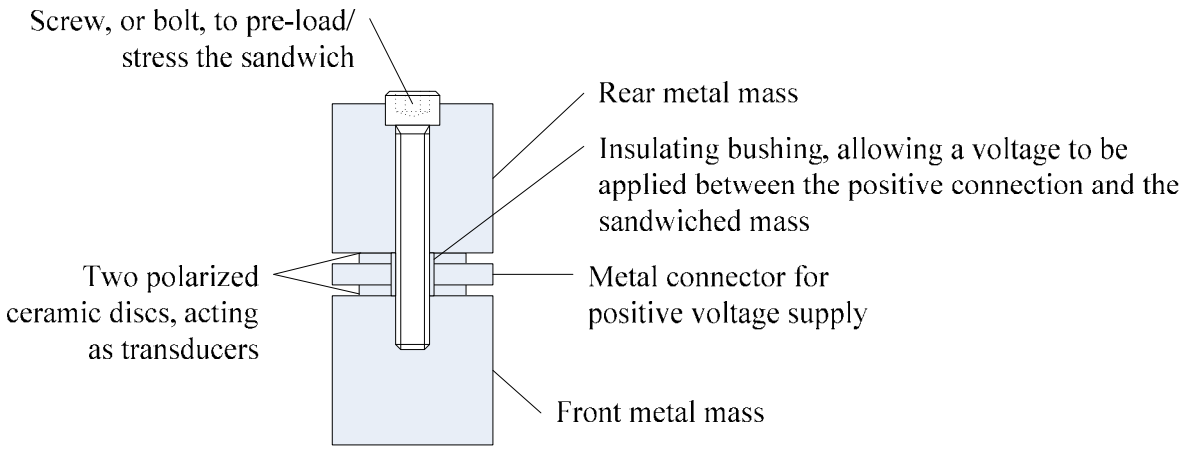
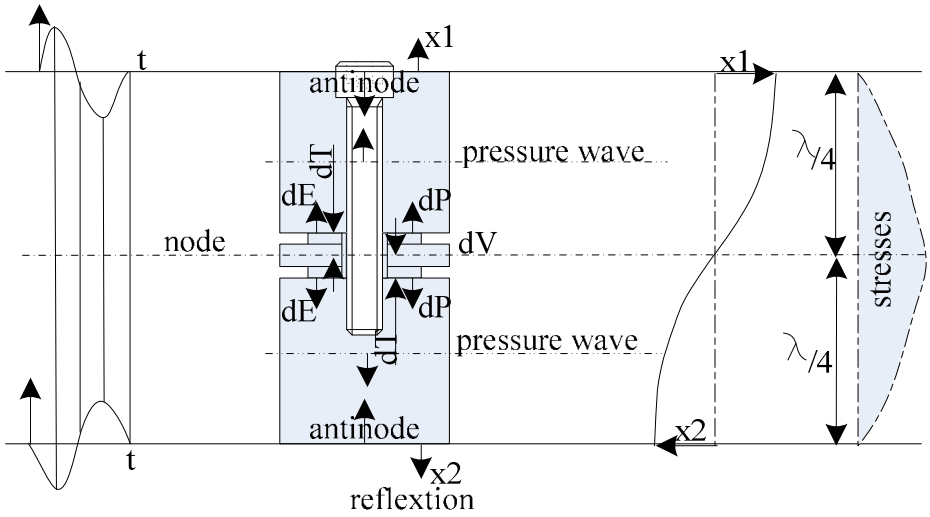


Figure 4.9 - Langevin's Triplet

Per the figure below, an alternating voltage (dV) is applied to the Triplet. There is a corresponding alternating electrical field (dE) and a corresponding alternating variation in thickness (dT) of the ceramic discs.

For each variation in thickness (dT) there is a corresponding variation in pressure (dP).



x1 = movement of face 1
x2 = movement of face 2

Figure 4.10 - Langevin's Triplet Displacement/Stresses

Notice that by applying an alternating voltage to the connector pressure waves are induced which, starting from the two ceramic discs, continuously propagate to each end of the Triplet.

If the length of each mass is dimensioned correctly, so that the frequency of longitudinal vibration of the bar corresponds exactly to its frequency of electrical excitation, the mass will become the source of stationary waves and will vibrate in resonance with the electrical excitation.

In this simple case the length of the mass, $L = \lambda / 2$ and $K = 1$. This is the operating principle of Langevin's Triplet.

4.5.4 Amplification

The vibrations of the emitter (or transducer) are of the order of 10 to 14 microns, measured peak to peak, depending on the type of generator used. These vibrations are not enough for cutting applications therefore they must be amplified.

To do this a half wavelength metal bar, matched to the natural frequency of the generator, is fixed to the emitter. In bars of this type the section (S1) for the first quarter wavelength is larger that the section (S2) for the second wavelength, so that an amplifying effect may be obtained.

If the bar was of constant section there would be no amplification effect as the second half would dampen or negate the first half. The amplification ratio is equal to the ratio of the sections, i.e. S1 / S2.

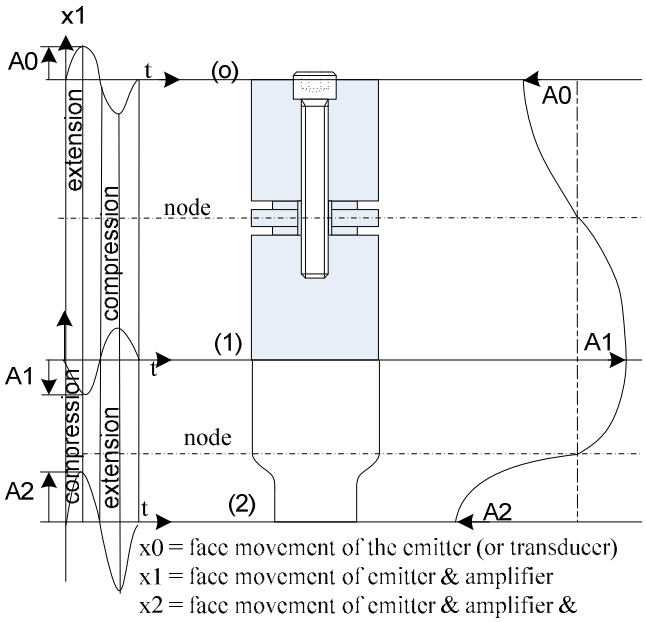


Figure 4.11 - Langevin's Triplet Movement w/ Emitter

Consider a half-wavelength metal bar and suppose the two quarter wavelengths have respective lengths of L1 and L2.

For the first quarter wavelength:		For the second quarter wavelength:	
L1 =	Length (λ_1 / 4)	L2 =	Length (λ_2 / 4)
M1 =	mass	M2 =	mass
d1 =	density	d2 =	density
C1 =	Sound velocity	C2 =	Sound velocity
S1 =	section	S2 =	section
A1 =	Amplitude at end of first quarter wave	A2 =	Amplitude at end of second quarter wave
x1 =	Movement at end of first quarter wave	x2 =	Movement at end of second quarter wave
x1 =	A1 * sin ωt	X2 =	A2 * sin ωt
V1 =	ω A1 cos ωt	V2 =	ω A2 cos ωt

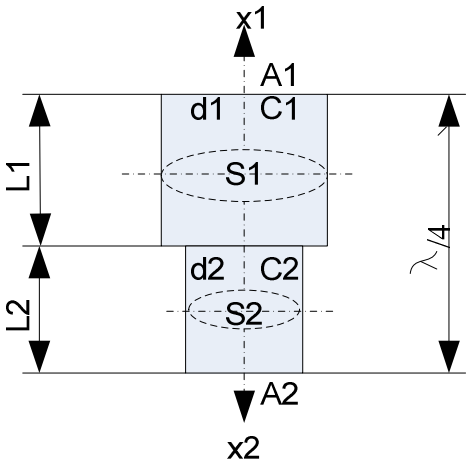


Figure 4.12 - Langevin's Triplet Length Relationship

Assuming frictional forces are negligible, when the bar vibrates in half wave lengths, it's kinetic energy is constant; it is equal to the energy which has been given out in the form of pulses to set the bar in motion.

If the frictional forces are zero, there is no dampening of the vibrations and the bar can thus vibrate indefinitely, its kinetic energy remaining constant.

$$Ec = \frac{1}{2} M1\, V1^2 + \frac{1}{2} M2\, V2^2 \text{ which derives to } M1\, V1 + M2\, V2 = 0$$

$$\frac{M1}{M2} = -\frac{V2}{V1} = \left|\frac{V2}{V1}\right| = \frac{\omega - A1\cos\omega t}{\omega - A2\cos\omega t} \text{ , let } \boxed{\frac{M1}{M2} = \frac{A2}{A1}}$$

$$M1 = S1\,\frac{\lambda 1}{4}(d1)$$

$$M2 = S2\,\frac{\lambda 2}{4}(d2)$$

$$\lambda 1 = C1\,(T)$$

$$\lambda 2 = C2\,(T)$$

$$\rightarrow \quad \frac{M1}{M2} = \frac{(S1)(C1)(D1)}{(S2)(C2)(D2)} = \frac{(S1)(Z1)}{(S2)(Z2)}$$

Resulting in …

$$\boxed{\frac{A2}{A1} = \frac{(Z1)(S1)}{(Z2)(S2)}}$$

This is the basic formula for the amplifier (booster) working in two quarter wavelengths. Consider again the case of an emitter coupled to a half wavelength bar, and comprising two different quarter wave sections S1 and S2.

For mechanical reasons, consider the bar to be machined or fabricated out of titanium. Using the second formula from above for similar materials, Z1 = Z2, resulting in:

$$\frac{A2}{A1} = \frac{S1}{S2}$$

Generally the choice for mass M1 is steel (Z = 46.7 x 10^6 MKS) or titanium (Z = 27 x 10^6 MKS). Titanium is also selected as mass M2 (horn) for the PPS.

For high amplitudes, a titanium mass is preferred because internal frictional losses are negligible up to amplitudes of 30 microns where steel begins to heat up noticeably at amplitudes of 10 microns. Use of titanium facilitates longer operating conditions as compared to steel as it does not retain mechanical heat.

Material selection and machining methods are also critical in terms of acoustic impedance, coefficient of internal friction, unidirectional effect and mechanical losses. For this reason titanium is the material of choice for the PPS horn and machining of the horn was unidirectional along its length.

In order to increase the frequency of a horn it must be lengthened. In testing and development it is ideal to fabricate high in terms of the final horn length as frequency may be lowered by removing material but it is obviously impossible to add material. For example, using a milling bit of 35mm, two cuts 2mm in depth can be made along the centerline equating to a reduction of 150 cycles per second.

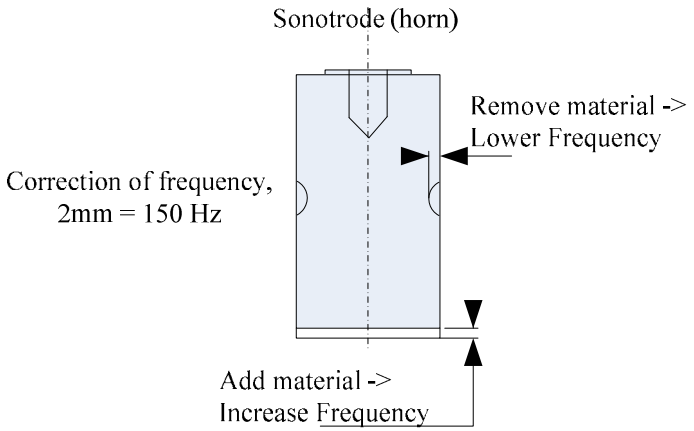
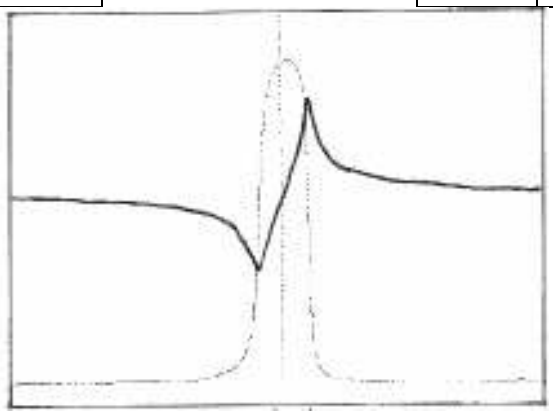


Figure 4.13 - Langevin's Triplet Displacement/Stresses

For the final shape of the horn utilized on the PPS, calculations were made for width and depth and then material was removed to both optimize the frequency and form the end cutting edge. Material of choice was titanium. A digital oscilloscope is used with induced voltage to define the following tuning curve.

A: Imp.	B: Phase	Center	40,000 Hz	MKR	40,050 Hz
A MAX	200.0 Kohm	Span	5000 Hz	MAG	564.699 ohm
B MAX	100.0 deg			Phase	74.8934 deg



4.6 Adjust

In this phase detailed engineering occurred before and concurrent with fabrication. Drawings were developed, reviewed and approved for fabrication. Overall assembly layouts were defined and updated as they are affected by higher level detailed engineering. Figure 4.14 shows the PPS assembly plan.

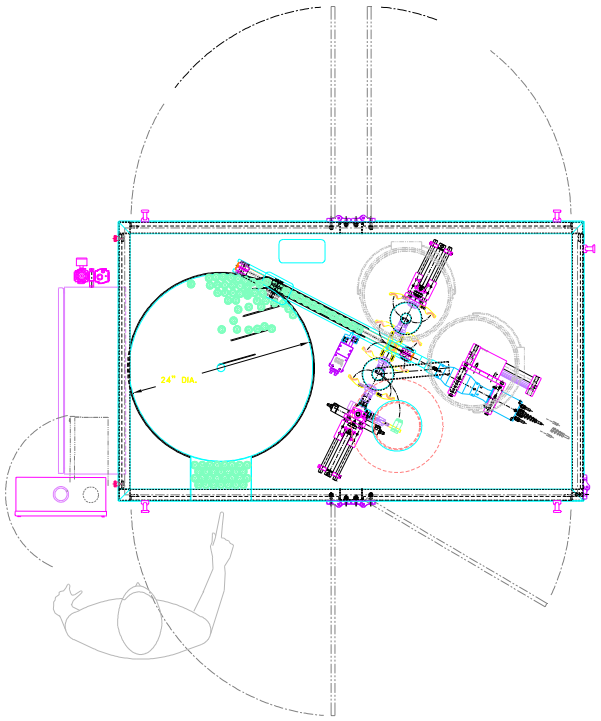


Figure 4.14 – PPS, Plan View

Component selection was finalized, automated motions were determined with associated mechanical engineering and control methodology. Adjustment occurred throughout this dynamic process to the point of hardware inspection and assembly.

Software selection and control system programming progress in parallel to mechanical assembly. Programming always includes an iterative process between myself, the programmer and the assemblers to finalize motion, function and fit.

Documentation was emphasized during this process in order to capture the “as built” system.

The engineering and fabrication activity ends at the point of fabrication with a the FAT (Factory Acceptance Test). This test comprised evaluation of the final assembly and functional testing of the system. Also included was verification that all documentation exists and represents the final system and includes material of construction information, “as built” drawings, component details and replacement information, software details, control system logic, operating information, utility requirements, and service and maintenance instructions. Approval of the FAT completed the initial system development and fabrication, and released the PPS for shipment.

4.7 Installation

Upon delivery of the PPS to the final location, installation started in a non-controlled area where a more extensive evaluation and testing continued. The system is portable by design so installation in this initial area is quickly completed. Compressed air was connected and the system is plugged into the available electrical power needed.

Control system components were verified as shown in Table 4.15.

Table 4.1 - Control System Cabinet Components

Description	Manufacturer	Part Number	Quantity
Nema 4X Enclosure	Hoffman	A24H2408SSLP	1
Subpanel	Hoffman	A24P24	1
Stainless Steel Enclosure	Hoffman	CSD1616SS	1
Subpanel	Hoffman	CP1616	1
Programmable Controller	Allen-Bradley	1762-L40BWA	1
Input Module	Allen-Bradley	1762-IQ16	2
Output Module	Allen-Bradley	1762-OB16	1
MCR Relay	Allen-Bradley	700-CF400ZJ	1
24V Power Supply	Automation Direct	PSP24-060C	1
125V Outlet	Automation Direct	FA-REC3	1
DC Motor Control	KB	KBIC-120	2
Dial Plate and Knob	KB	9832	2
Plug-In Horsepower Resistor	KB	0.51 ohm	1
Plug-In Horsepower Resistor	KB	0.25 ohm	1
Counter	Red Lion	APLT0800	1
Timer	Crouzet	88 857 005	1
8-Pin Reverse Mount Socket	IDEC	SR6P-M08G	1
Stack Light Base	Allen-Bradley	855EBCBC	1
24V Tone Module	Allen-Bradley	855EB24SA3	1
24V Stack Light	Allen-Bradley	855E24DN3	2
E-Stop Button	Allen-Bradley	800TFXQ24RA1	1
2-Position Selector Switch	Allen-Bradley	800TH2D1	3
3-Position Selector Switch	Allen-Bradley	800TJ91A	8
Push Button	Allen-Bradley	800TB2D1	3
Solid State Relay	Crouzet	84130104	2
Disconnect Contactor	ABB	OT16ET3	1
Disconnect Handle	ABB	OHY2RJ	1
5A Circuit Breaker	ABB	S201-K5	2
1A Circuit Breaker	ABB	S201-K1	1
2A Circuit Breaker	ABB	S201-K2	2
15A Circuit Breaker	ABB	S201-K15	2
Magnet Sensor	Banner	SI-MAG2SM w/30	7
Coded Magnet	Banner	SI-MAG2MM	7
Reflective Fiber Unit	Keyence	FU-67TG	4
Amplifier	Keyence	FS-V21RP	4
Relay	Sky	SKAP-2C	2

After documentation and system inspection was completed the initial desire was to begin research on the ultrasonic cutting of every bottle size, type and material that will be presented in routine processing.

4.8. Changeover

But first, the PPS must be changed over to process the target bottle size. This process is required before each pooling process. Recall that bottles processed for a single campaign are identical and are processed as a single lot. Bottles containing different product are not mixed together and those of different sizes or configurations, i.e. round and oval, are not intermingled.

Following are the changeover procedures developed.

4.8.1 Infeed Turntable – Bottle Discharge Changeover

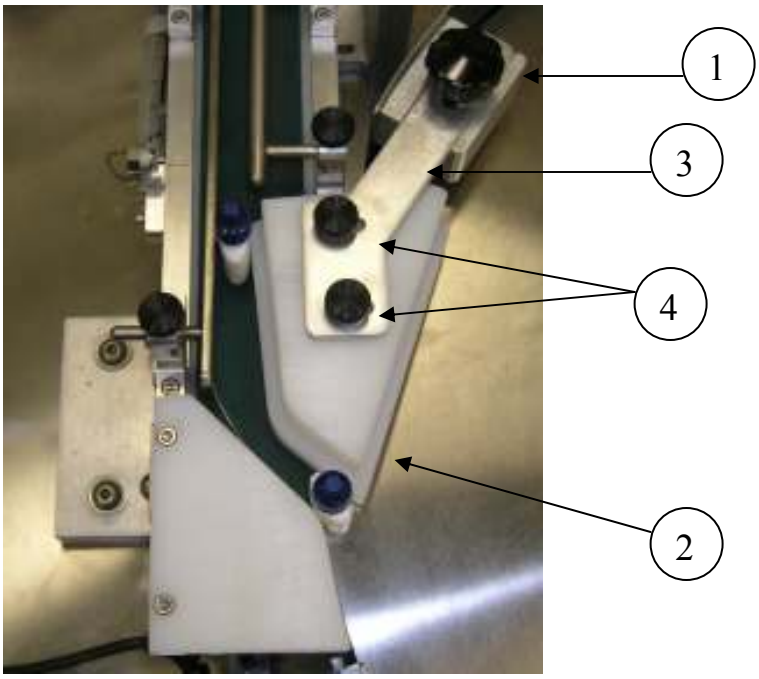


Figure 4.15 – Bottle Discharge Changeover

1. Remove two knobs (item 4).
2. Replace bottle discharge (item 2) and replace with discharge for new bottle size.
3. Replace two knobs (item 4).
4. Adjust bottle discharge (item 2) as needed for new bottle size, and tighten knobs.
5. Loosen large knob (item 1) to slide mounting bar (item 3) for further adjustment as needed.
6. Tighten large knob (item 1).
7. Assure all knobs and screws are secure.

4.8.2 Conveyor – Guide Rail Adjustment

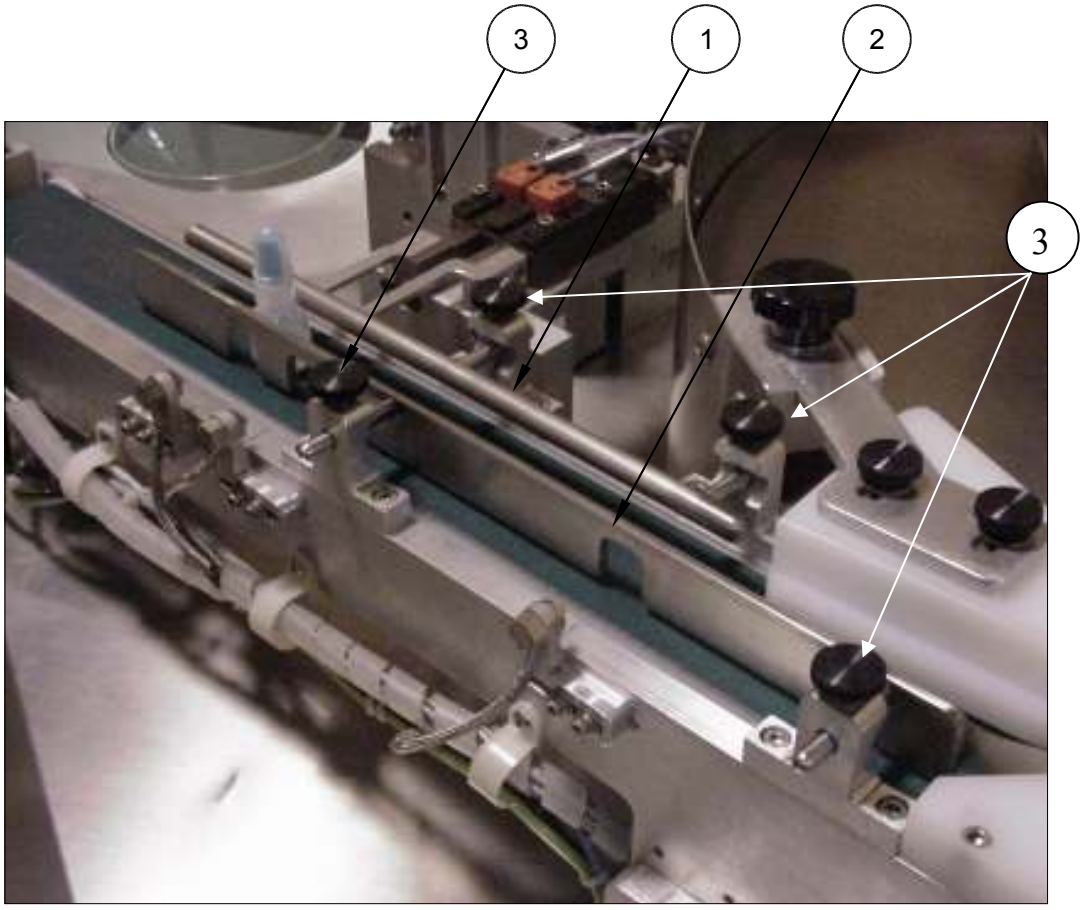


Figure 4.16 – Guide Rail Adjustment

1. Loosen knobs (item 3) in 4 places.

2. Move guide rails (items 1 and 2) as needed for the new bottle size.

3. Tighten knobs to secure guide rails.

4.8.3 Conveyor – Bottle Stop Changeover

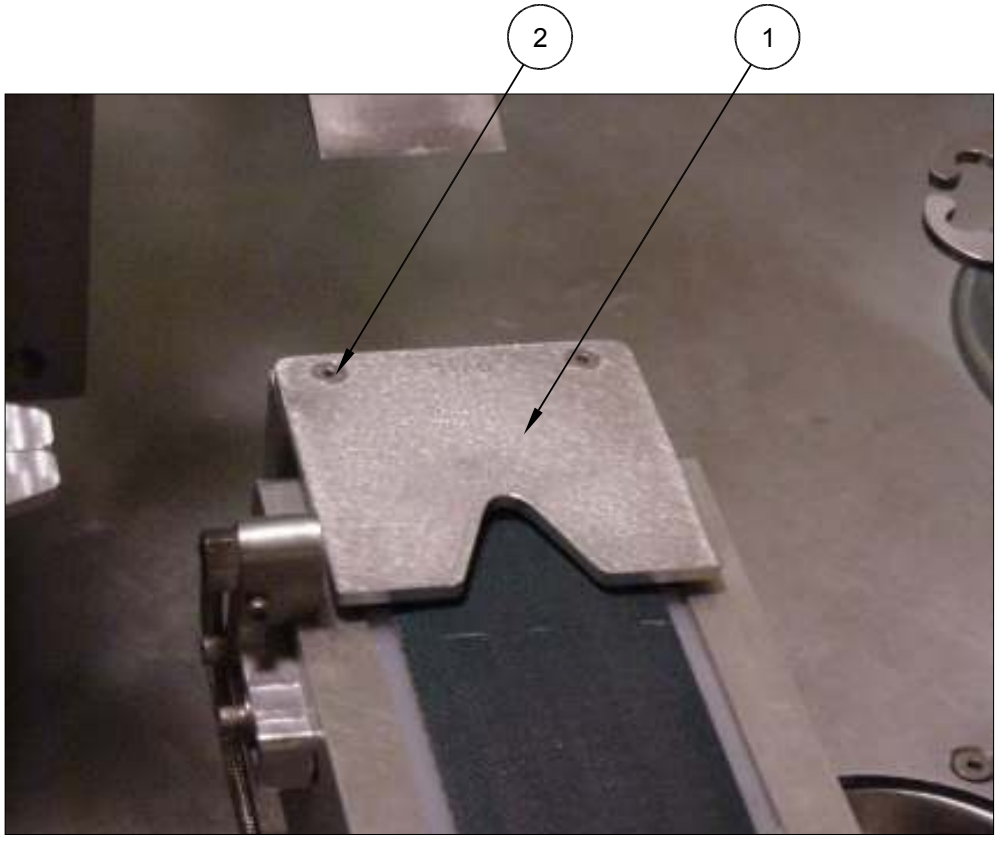


Figure 4.17 – Bottle Stop Changeover

1. Remove flat head socket cap screws (item 2).

2. Replace stop plate (item 1) with stop plate for new bottle size.

3. Replace (2) screws.

4.8.4 Singulator Changeover

Figure 4.18 – Singulator/Escapement Stop Changeover

1. Remove socket head cap screws (item 3) from left stop.

2. Replace left stop (item 1) with the stop for the new bottle size.

3. Replace socket head cap screws.

4. Remove socket head cap screws (item 4) from right stop (item 2).

5. Replace right stop (item 2) with the stop for the new bottle size.

6. Replace socket head cap screws.

4.8.5 Bottle Cap Station – Gripper Change and Height Adjustment

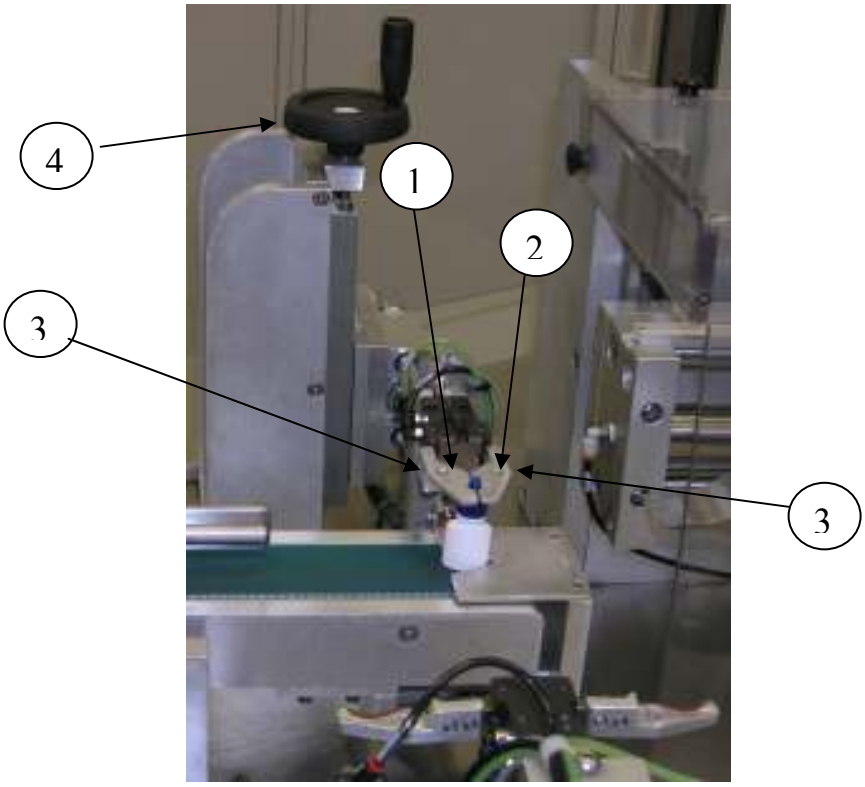


Figure 4.19 – Bottle Cap Station

1. Remove socket head cap screws (item 3) from left gripper finger.
2. Replace left gripper (item 1) with left gripper finger for new bottle size.
3. Replace socket head cap screws.
4. Remove socket head cap screws (item 3) from right gripper finger.
5. Replace right gripper (item 2) with gripper finger for new bottle size.
6. Replace socket head cap screws.
7. Adjust the height for the new gripper size using the hand wheel (item 4).

   See the height adjustment chart.

4.8.6 Bottle Gripper – Gripper Changeover and Height Adjustment

Figure 4.20 – Bottle Gripper Station

1. Remove socket head cap screws (item 3) from left gripper finger (item 1).

2. Replace left gripper finger with left finger for new bottle size.

3. Replace socket head cap screws.

4. Remove socket head cap screws from right gripper finger (item 2).

5. Replace right gripper finger with right finger for new bottle size.

6. Replace socket head cap screws.

7. If the changeover will accommodate the 4 oz. bottle, then move the horizontal mounting plate (item 4) to top of slots in vertical plate (item 5).
    i. Loosen socket head cap screws at front of vertical plate.
    ii. Move horizontal plate, including the rotary actuators and gripper, to top of slots.
    iii. Tight socket head cap screws.

4.8.7 Ultrasonic Head Assembly – Height Adjustment

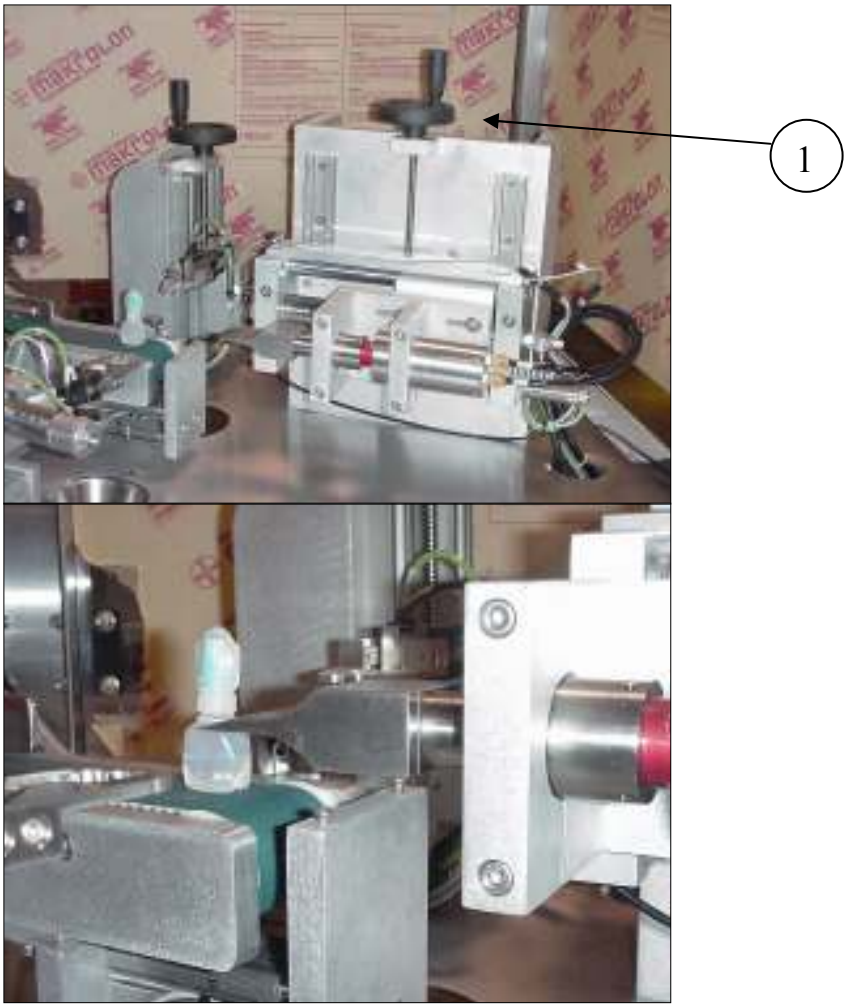


Figure 4.21 – Ultrasonic Cutter (Horn) Station

1. Use hand wheel (Item 1) to move ultrasonic head assembly into position for new bottle size.

2. The cutting edge must be in line with the neck of the bottle and still be able to clear the gripper fingers of the bottle gripper. See the height adjustment chart.

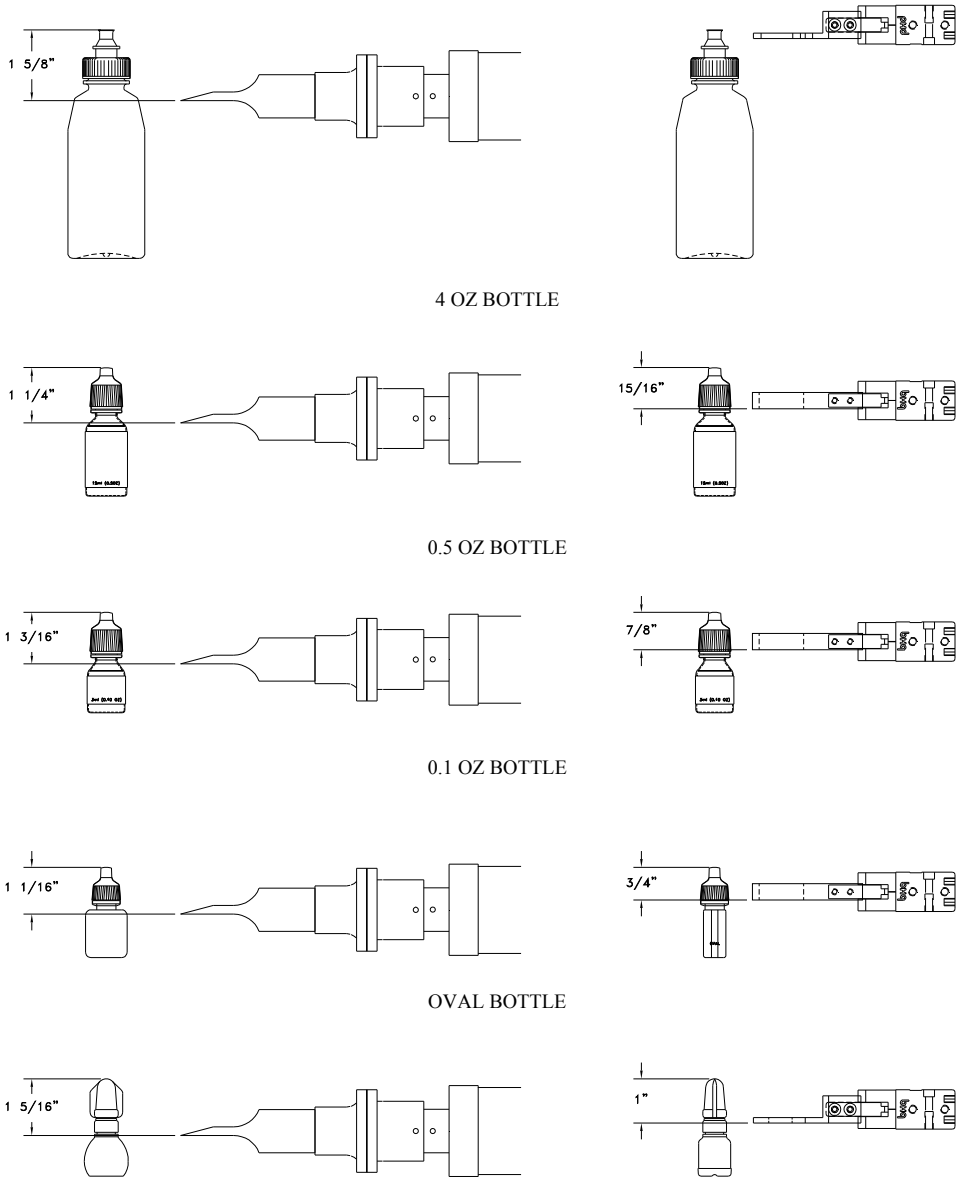


Figure 4.22 – Ultrasonic Head Assembly Height Adjustment Chart

4.8.8 System Start-Up

Using the Operator Control Panel, panel face view as follows:

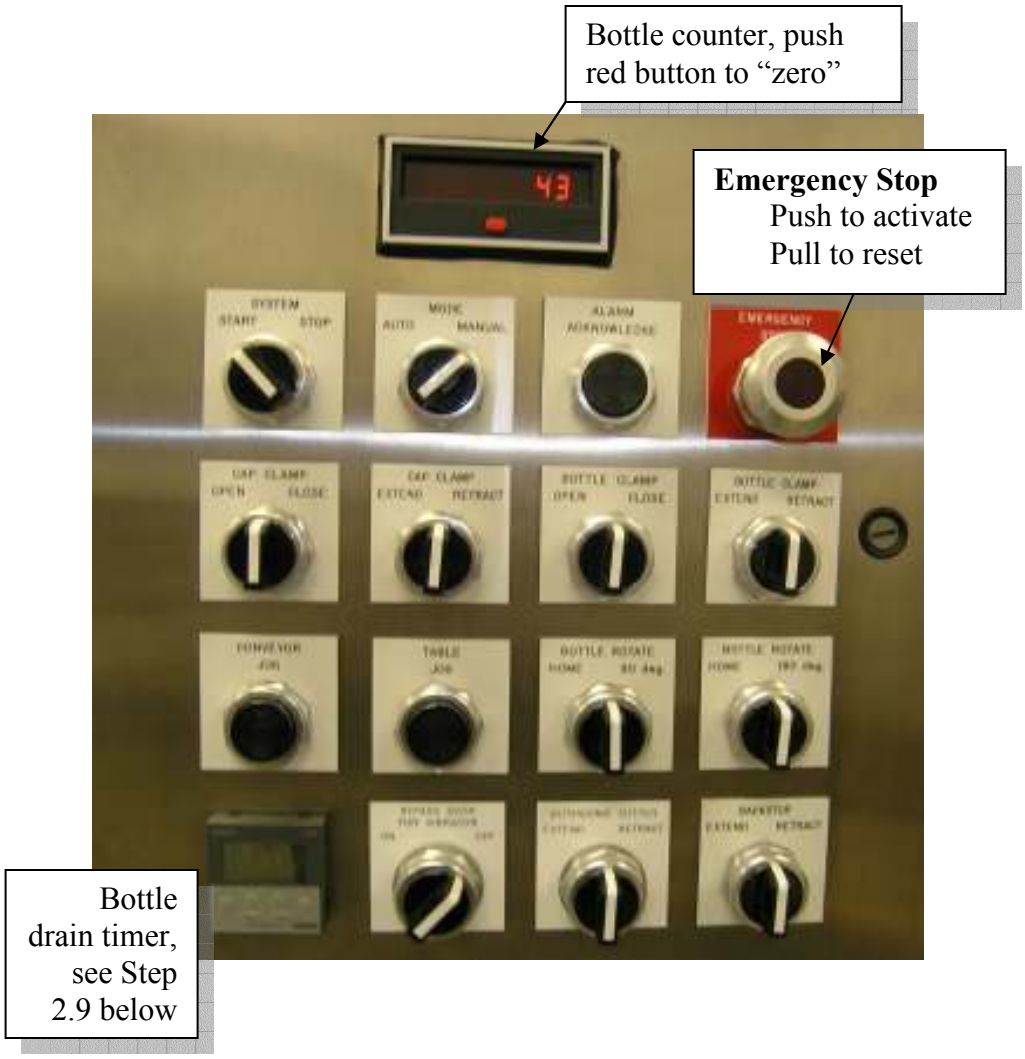


Figure 4.23 – Operator Panel

4.8.9 Alignment Verification

Using the bottle to be processed.

Place the

to “MANUAL” and set

to “START”.

Using the switches on the operator panel process the bottle manually, step by step, through each station to assure flow, proper cut line and proper gripping

4.8.10 Normal Start-Up

Assure electric power plug is plugged into compatible receptacle.

Assure power cord is routed flat across floor with no raised portions where a foot or piece of equipment can become caught.

Connect high pressure compressed air line from filtered use point to Product Pooling System air supply connection.

Confirm regulated air supply is set to at approximately 75 psig

Rotate main power switch to “ON” position.

Note that green light above operator panel should illuminate steady.

Using the Operator Panel; set to “AUTO” and set to “START”.

Load bottles onto In Feed table (also see section 2.10) and observe bottles flowing into conveyor, through the singulator, to the bottle station (gripping and cutting), through pooling station (confirm bottle drain time) and finally, disposal of components.

Bottle drain time may be varied using the “Bottle Drain Timer”. This setting may be adjusted at any time before, during or after processing. The last value entered is retained until is changed.

In Process Display, current displayed value = 3.50 seconds

Setpoint Display
To change the setting - Depress the touch panel button under the number to be changed. The number will then increase upward (e.g. 0,1,2,…9). Releasing the button registers the new value.

4.8.11 Single Bottle Feed

The system is equipped with a feature to enable a user to individually place bottles onto the feed conveyor for processing, thus avoiding use of the rotary in feed table. This use is likely to occur when bottles must be vibrated in some way prior to processing or when they may be unstable (e.g. oval) on the rotary table.

For this functionality the “BYPASS DOOR FOR VIBRATOR” Switch” on the Operator panel must be set from “OFF” to “ON”.

After processing return the switch to the normal “ON” position.

4.8.12 Normal Shutdown

Clear all components and collected product from the system.

Using the Operator Panel; set

to “MANUAL” and set

to “STOP”.

Rotate main power switch to “OFF” position.

Compressed air service may remain on or turned off, safely isolated at source, and disconnected.

4.8.13 System Alarms

The following alarms may occur during normal operations. Expected user corrective action to recover is also noted.

Table 4.2 – System Alarms

System Created Conditions		
Abnormal Condition	Expected System Response	Expected Operator Action Required to Recover
Bottle Jam at Singulator	Machine continues to run, audible alarm sounds, red light illuminates.	1. Press “Alarm Acknowledge” pushbutton to silence audible alarm. 2. Turn “Mode” selector switch to “Manual”. 3. Open access door and clear jam condition. 4. Turn “Mode” selector switch to “Auto”.

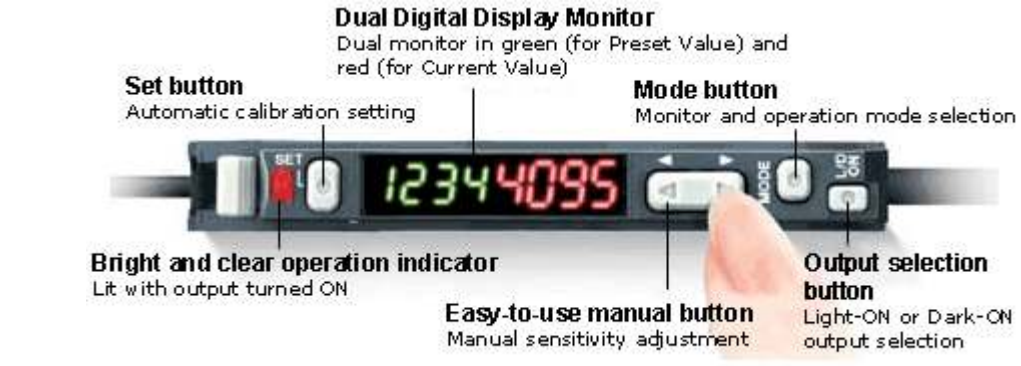
Table 4.2 - continued

Machine continues to cycle with no bottle present at bottle grip station (PE1)	PPS cycles while singulator does not release bottle or no bottles are in system	1. Turn “Mode” selector switch to “Manual”. 2. Turn “System” selector switch to “Stop”. 3. Open access door and check lens of PE1, remove any accumulated particles or interference with view area. 4. If problem persists, open lower access door beneath infeed table and check response sensitivity of sensor PE1 with bottle present and not present, adjust as needed. 5. Close all access doors. 6. Turn “Mode” selector switch to “Auto”. 7. Turn “System” selector switch to “Start”.
Operator Induced Errors		
Error/Fault Condition	Expected System Response	Expected Operator Action Required to Recover
Operator Side Access Door Open	Machine stops and devices return to their home position. Note: If bottle is gripped and partially in process, it will be dropped	1. Close access door. 2. System resumes in normal, auto, operation.
Service Access Door Open	Machine stops (Reset lights)	1. Close access door. 2. System resumes in normal, auto, operation.

Table 4.2 - continued

Supplied Utility Disruptions		
Error/Fault Condition	Expected System Response	Expected Operator Action Required to Recover
Main Electrical Power Loss or Supply Turned Off	Machine stops - all control panel lights go out.	1. Restore electrical power. 2. System resumes in normal, auto, operation.
Disconnect or turn off Compressed Air Supply (while operating)	1. Machine conveyor and turntable (electrically powered items) continue to operate. 2. Air powered device action stops. 3. Audible alarm sounds 4. Red light illuminates	1. Press “Alarm Acknowledge” pushbutton to silence audible alarm. 2. Turn “Mode” selector switch to “Manual”. 3. Turn “System” selector switch to “Stop”. 4. Restore compressed air supply. 5. Using switches on control panel return all devices to their home positions being careful to remove any bottles currently in process. 6. Turn “Mode” selector switch to “Auto”. Turn “System” selector switch to “Start”.

Additionally sensor settings need to be determined. The PPS is equipped with four sensing photo eyes (designated as PE) along the flow path of bottles being processed. Photo eyes, in this case fiber optic sensors, sense by emitting a light beam and measuring the response off the reflective surface of the bottle being sensed. The sensor displays the value detected in addition to the current setpoint.



Preset Value and Current Value
Preset Value can be changed while monitoring the amount of light received.

Peak Value and Bottom Value
The Hold function makes it possible to simultaneously display both peak and bottom values.

Figure 4.24 - Keyence® Fiber Optic Sensor, FV20 Series

The setpoint is adjusted up or down to exceed the value detected to assure the control system bit is set to high or on when the bottle is in position. Following are the sensors and relative locations on the PPS.

PE1 – Bottle at Gripper Station

PE2 – Bottle at Singluator Release

PE3 – Bottle at Entry to Singulator

PE4 – Conveyor Full Sensor (stops rotation of turntable)

Table 4.3 details the vendors specifications for the fiber optic sensors as installed on the PPS.

Table 4.3 - Digital Display Amplifier Specifications

Type	**Main unit**
Model PNP	**FS-V21RP**
Light source	Red LED
Response time	250µs (FINE)/500µs (TURBO)/1ms (SUPER TURBO)/4ms(ULTRA TURBO)/ 500µs (HIGH RESOLUTION)/50µs (HIGH SPEED)
Operation mode	Light-ON/Dark-ON (switch-selectable)
Detection mode	Light intensity/rising edge/falling edge
Timer function	Mode:Timer OFF/OFF-delay timer/ON-delay timer/One-shot timer, selectable Variable range:1 to 500ms [1 to 30ms (in 1ms increments), 30 to 50ms (in 2ms increments), 50 to 200ms (in 10ms increments), 200 to 500ms (in 50ms increments)] Accuracy:±10% of the Preset Value
Control output	NPN or PNP 100 mA max. (40VDC max), Residual voltage : 1Vmax.
Power supply	12 to 24VDC ±10% , ripple: 10% max.
Ambient light	Incandescent lamp: 20,000 lux max. , Sunlight: 30,000 lux max.
Ambient temperature	-10°C to +55°C (14 to 131°F), No condensation
Relative humidity	35 to 85%, No condensation
Vibration resistance	10 to 55 Hz, 1.5-mm double amplitude, each in X, Y, and Z directions for two hours
Shock resistance	500 m/s² Three times each in X, Y, and Z directions

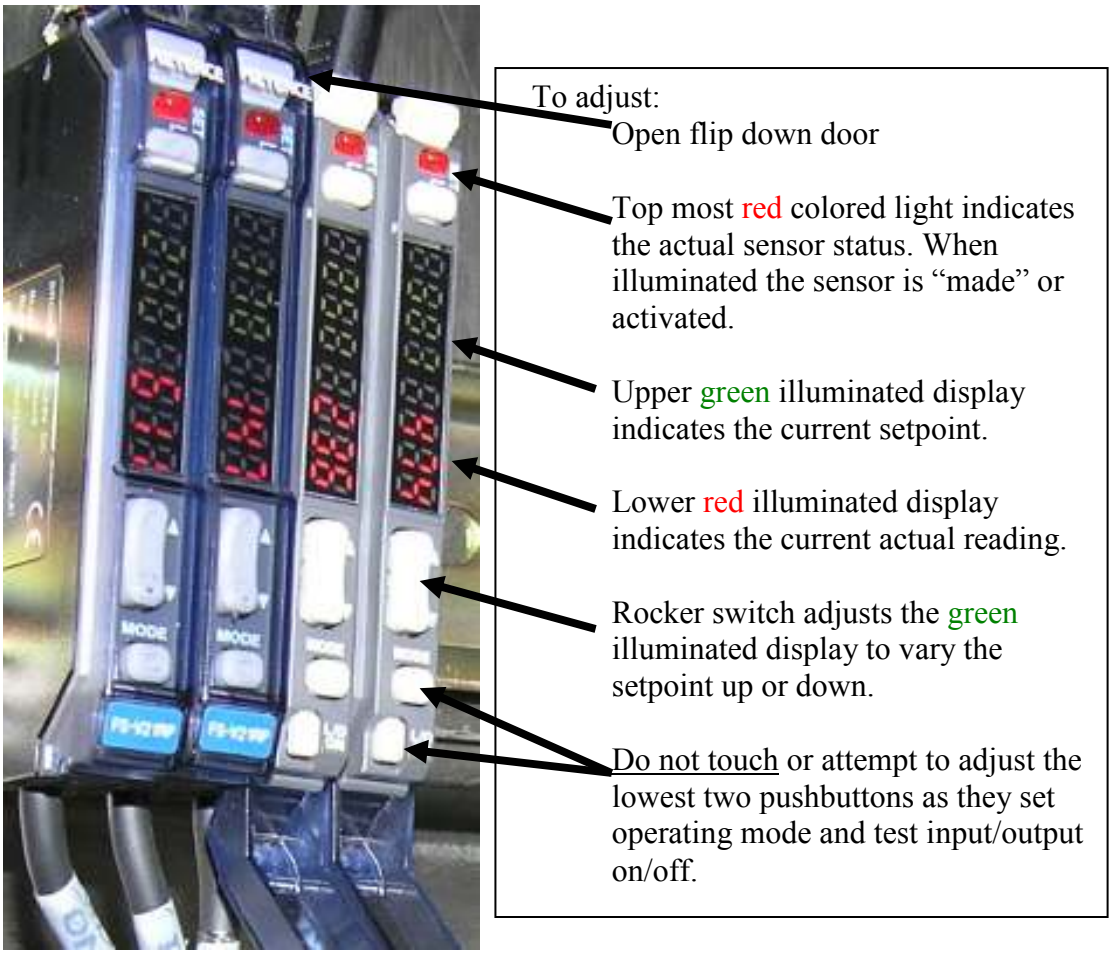


Figure 4.25 - PPS Photo eye (PE) Adjustment

Other sensors installed on the PPS are motion sensors which detect movements such as rotation and extension or retraction. The sensors do not require any routine adjustment and operate based on the Hall effect.

In 1879 Edward Hall placed a thin layer of gold in a strong magnetic field. He then connected a battery to the opposite sides of this film and measured the current flowing through it. He discovered that a small voltage appeared across this film. This

voltage was proportional to the strength of magnetic field multiplied by the current. This observed effect bears his name.

For many years the Hall effect was not used in practical applications because the generated voltage in the gold film was extremely low. However, in the second half of the 20th century the mass production of semiconductor chips started. Chips based on the Hall effect became inexpensive and widely available.

The Hall effect IC (integrated circuit) is a very small chip which includes many transistors. It consists of a thin layer of silicon as a Hall generator (which works better than gold) and several transistor circuits: to amplify the Hall voltage to a necessary level; to trigger output voltage with its growth; and to provide stable work regardless of the power supply voltage changes.

4.9 Power and Energy

The objective of this phase of research was to determine, test and baseline both power and energy related to the ultrasonic cutting of the bottles and related materials, to be processed.

Ultrasonic power is the acoustic energy of sound per unit time, usually measured in watts (W), 1 W being 1 joule/s.

Intensity of sound is the acoustic energy (joule) per unit time (second) and unit area (square meter). The intensity of sound is thus the acoustic power per unit area, measured in W/m^2. The intensity is determined by the amplitudes or excursions of the particles conducting the waves; the larger the amplitudes of oscillation, the higher the

intensity. The actual relationship is $I = p^2/2Z$, where I is intensity, p is pressure amplitude, and Z is acoustic impedance.

Acoustic impedance is the property of material causing resistance to the propagation of ultrasound. Acoustic impedance is defined as $Z = r\ c$, where r is the material density, and c is the propagation velocity of ultrasound in the material.

Ultrasound propagation is dependent partly upon the particle mass (which determines the density of the material), partly upon the elastic forces binding the particles together (which determine the propagational speed of sound). A fraction of the ultrasound is reflected whenever there is a change in acoustic impedance. The larger the change in acoustic impedance, the larger the fraction reflected.

Longitudinal wave is a waveform transmitted through a medium where the particles of the medium oscillate in the direction of the wave propagation. Sound propagates as longitudinal waves. A longitudinal wave is produced when a vibrator, e.g. a piezoelectric crystal in an ultrasound transducer, transmits it back and forth oscillation into a continuous, elastic medium. The particles of the medium are made to oscillate in the direction of the wave propagation, but are otherwise stationary. The wave propagates as bands of compression and rarefaction. One wavelength is the distance between two bands of compression, or rarefaction. Maximum compression corresponds to maximum pressure.

Piezoelectric or piezoelectric effect, the phenomenon that certain crystals change their physical dimensions when subjected to an electric field, and vice versa;

when deformed by external pressure, an electric field is created across the crystal (from the Greek word piezein = pressure). Piezoelectric crystals are used in ultrasound transducers to transmit and receive ultrasound.

Recall that energy is one of the quantities which in a closed physical system remains constant. This fundamental observation is termed the law of conservation of energy. fundamental physical quantity characterizing particles, waves and entire physical systems. In physics several types of energy are distinguished: gravitational and mechanical energy, electromagnetic energy, thermal energy, nuclear energy and chemical energy.

Ultrasonic energy is mechanical energy measured in units of joule (J). The unit of joule (j) derives from a British physicist, James Prescott Joule (1818-1889). One joule equals the work done by a force of one newton, acting through a distance of one meter (1 J = 1 Nm or 1 J = 1 kg m^2/s^2).

4.9.1 Materials Tested

Ultrasonic power and energy testing proceeded with the accumulation of materials encompassing those to be processed. Included was a variety of round and oval bottles varying in height, diameter and material of construction.

Materials of construction are thermoplastics formed via injection molding processes. Thermoplastics are those that can be recycled or remelted and processed again as compared with thermosetting plastics which, once formed, cannot be remelted and used again.

The four materials comprising the range of those typically used for pharmaceutical packaging are SPP, LDPE, HDPE and PET.

Syndiotactic polypropylene (SPP) - is a form of polypropene (PP), a thermoplastic polymer, used in a wide variety of applications, including food packaging, textiles, plastic parts and reusable containers of various types. The syndiotactic structure produces a unique set of physical properties such as exceptional clarity and gloss, a melting point of 128 C, low level of extractables, and are much softer than conventional isotactic polypropylene.

Low Density Polyethylene (LDPE) - LDPE resin is easy to process and improves product performance because it offers excellent printability, strength, tear resistance and elasticity. It is useful for producing a variety of products including liners, bags, shrink and lamination films, extrusion coatings and caps and closures. It is durable enough to produce a variety of products such as power cables and toys.

High Density Polyethylene (HDPE) - HPDE resin is useful for applications that require toughness, rigidity and strength, making it a good choice for blow molding and injection molding applications. HDPE pipe resin offers toughness and stress crack resistance making it a good choice for pipe extrusion. HDPE resin offers strength and processability that is essential for injection molding applications.

Polyethylene terephthalate (PET) - A saturated, thermoplastic, polyester resin made by condensing ethylene glycol and terephthalic acid. It offers very fast cycle times for injection molding processing and is exceptionally rigid, extremely hard, wear-

resistant, dimensionally stable, resistant to chemicals, and has good dielectric properties. It also has very low moisture absorption characteristics.

A comparison of like properties of these materials are shown in Table 4.4.

Table 4.4 – Material Property Comparison

SPP - Syndiotactic Polypropylene, Thermoplastic

Properties	Value	Comments
Physical		
Density, g/cc	0.88	None.
Mechanical		
Tensile Strength, Ultimate, MPa	15.2	None.
Elongation at Break, %	250	None.
Elongation at Yield, %	11	None.
Tensile Modulus, GPa	0.483	None.
Thermal		
Melting Point, °C	130	None.

Low Density Polyethylene (LDPE), Thermoplastic

Properties	Value	Comments
Physical		
Density, g/cc	0.917 - 0.965	Average = 0.933 g/cc
Mechanical		
Tensile Strength, Yield, MPa	7.3 - 28.6	Average = 14.8 Mpa
Elongation at Break, %	50 - 910	Average = 510%
Elongation at Yield, %	7.5 - 30	Average = 17.2%
Tensile Modulus, GPa	0.15 - 1	Average = 0.32 Gpa
Thermal		
Melting Point, °C	122 - 136	Average = 130°C

High Density Polyethylene (HDPE), Thermoplastic

Properties	Value	Comments
Physical		
Density, g/cc	0.918 - 1.4	Average = 0.956 g/cc
Mechanical		
Tensile Strength, Yield, MPa	2.4 - 31.7	Average = 25.2 Mpa
Elongation at Break, %	10 - 1500	Average = 380%
Elongation at Yield, %	6.9 - 15	Average = 9.5%
Tensile Modulus, GPa	0.18 - 1.6	Average = 0.911 Gpa
Thermal		
Melting Point, °C	110 - 135	Average = 130°C

Table 4.4 - continued
PET - Polyethylene Terephthalate, Thermoplastic

Properties	Value	Comments
Physical		
Density, g/cc	1.32	None.
Mechanical		
Tensile Strength, Yield, MPa	55	50 mm/min
Elongation at Break, %	50	minimum
Elongation at Yield, %	3.8	None.
Tensile Modulus, GPa	2.47	1 mm/min
Thermal		
Melting Point, °C	243	None.

4.9.2 Test Results

Power and energy data were collected for each of the four materials to assure the materials can be successfully processed and to gather baseline data for the perfomance of the ultrasonic generator and associated transducer and horn. Also included in the testing were representative assortments of round and oval bottles in each material.

For each run parameters and cycle time was recorded and data collected, plotted and compared.

Table 4.5 - SPP Test Run, Power and Energy

		7.5ml SPP Oval	
Bottle Tested	=	(clear)	
Horn Height	=	58	mm
Drain Time	=	4.00	seconds
Quantity Processed	=	170	
Number of Rejects	=	0	
PE Settings			
PE 1	=	400	
PE 2	=	210	
PE 3	=	190	
PE 4	=	400	
Measured Cycle Time	=	14.4	seconds
Avg. Cycle Time from Data	=	0:00:17	seconds
MIN. Cycle Time from Data	=	0:00:14	seconds
MAX. Cycle Time from Data	=	0:02:28	seconds

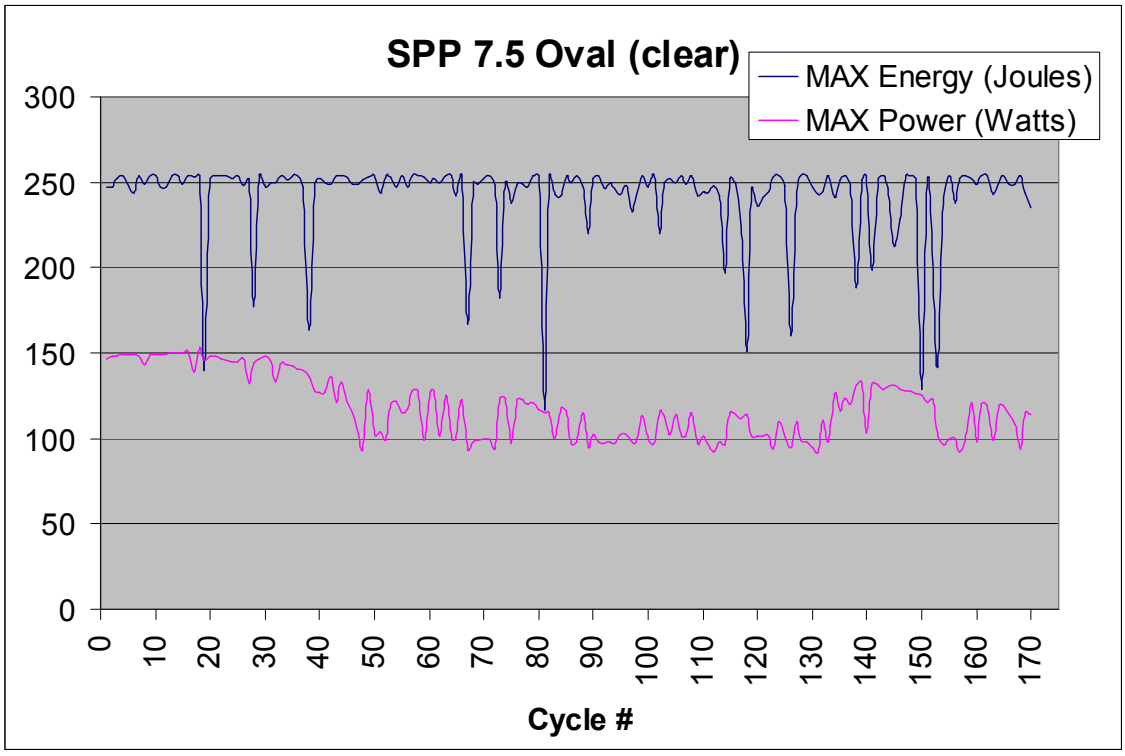


Figure 4.26 – SPP Power and Energy Chart

Table 4.6 - LDPE Oval Test Run, Power and Energy

Bottle Tested	=	4ml LDPE Oval (white)	
Horn Height	=	52	mm
Drain Time	=	4.00	seconds
Quantity Processed	=	201	
Number of Rejects	=	0	
PE Settings			
PE 1	=	1045	
PE 2	=	280	
PE 3	=	239	
PE 4	=	538	
Measured Cycle Time	=	14.4	seconds
Avg. Cycle Time from Data	=	0:00:15	seconds
MIN. Cycle Time from Data	=	0:00:14	seconds
MAX. Cycle Time from Data	=	0:00:19	seconds

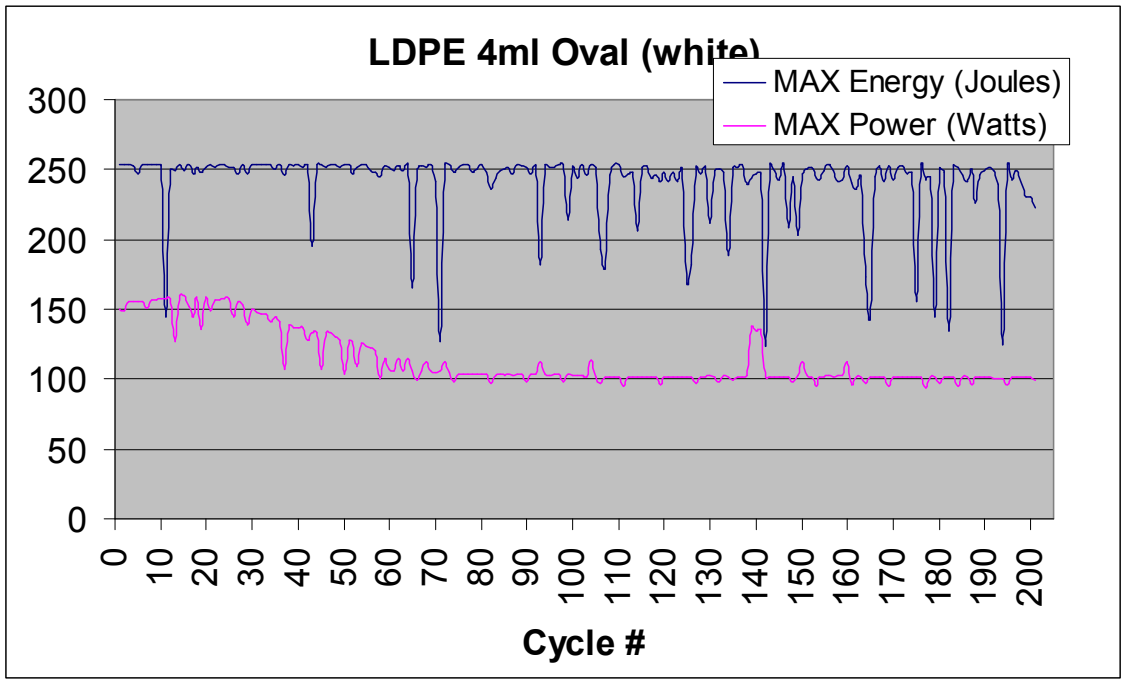


Figure 4.27 - LDPE(oval) Power and Energy

Table 4.7 - HDPE Oval Test Run, Power and Energy

Bottle Tested	=	4 oz. HDPE (white)	
Horn Height	=	25	mm
Drain Time	=	4.00	seconds
Quantity Processed	=	194	
Number of Rejects	=	0	
PE Settings			
PE 1	=	1045	
PE 2	=	280	
PE 3	=	239	
PE 4	=	538	
Measured Cycle Time	=	14.4	seconds
Avg. Cycle Time from Data	=	0:00:14	seconds
MIN. Cycle Time from Data	=	0:00:11	seconds
MAX. Cycle Time from Data	=	0:00:28	seconds

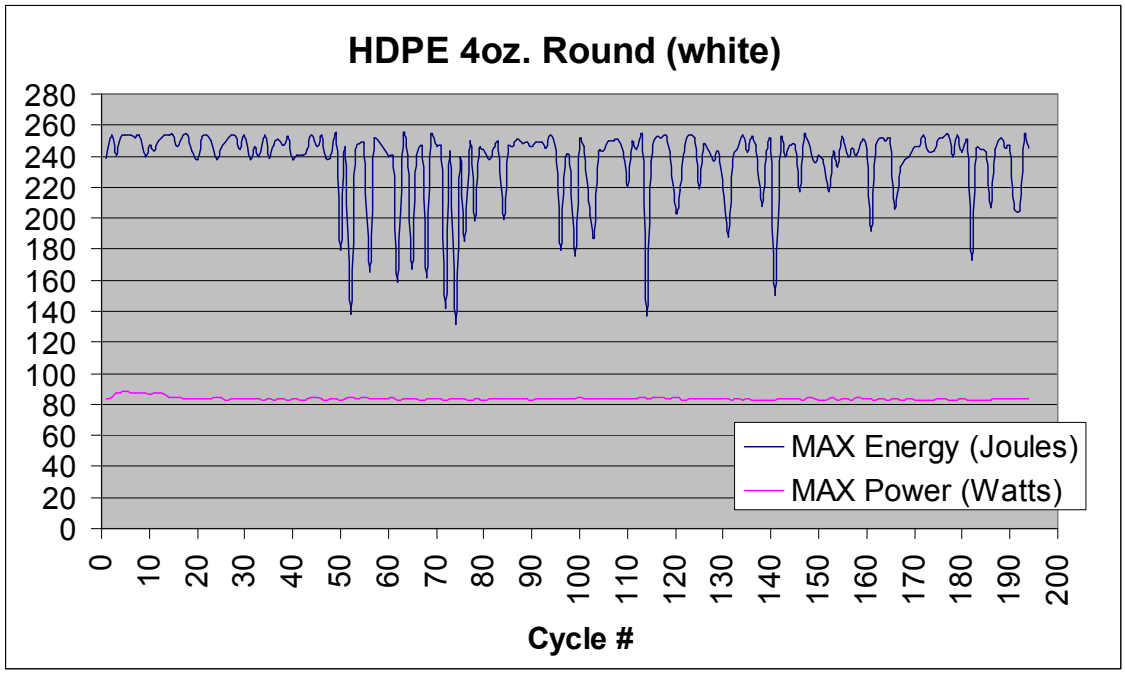


Figure 4.28 - HDPE Power and Energy

Table 4.8 - PET Oval Test Run, Power and Energy

Bottle Tested	=	2 oz. PET Round (white)	
Horn Height	=	180	mm
Drain Time	=	4.00	seconds
Quantity Processed	=	208	
Number of Rejects	=	0	
PE Settings			
PE 1	=	1045	
PE 2	=	280	
PE 3	=	239	
PE 4	=	538	
Measured Cycle Time	=	14.4	seconds
Avg. Cycle Time from Data	=	0:00:14	seconds
MIN. Cycle Time from Data	=	0:00:12	seconds
MAX. Cycle Time from Data	=	0:00:28	seconds

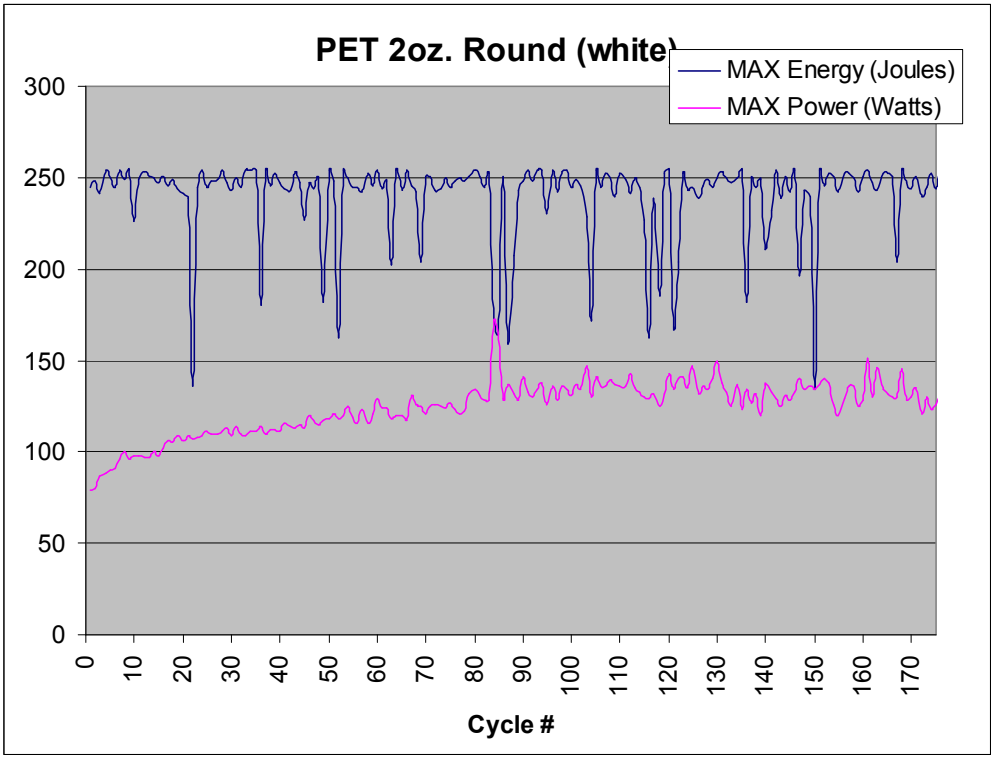


Figure 4.29 - PET Power and Energy

Table 4.9 - LDPE Round Test Run, Power and Energy

Bottle Tested	=	8ml LDPE Round (clear)	
Horn Height	=	150	mm
Drain Time	=	2.00	seconds
Quantity Processed	=	147	
Number of Rejects	=	0	
PE Settings			
PE 1	=	1045	
PE 2	=	280	
PE 3	=	239	
PE 4	=	538	
Measured Cycle Time	=	13.2	seconds
Avg. Cycle Time from Data	=	0:00:14	seconds
MIN. Cycle Time from Data	=	0:00:03	seconds
MAX. Cycle Time from Data	=	0:01:36	seconds

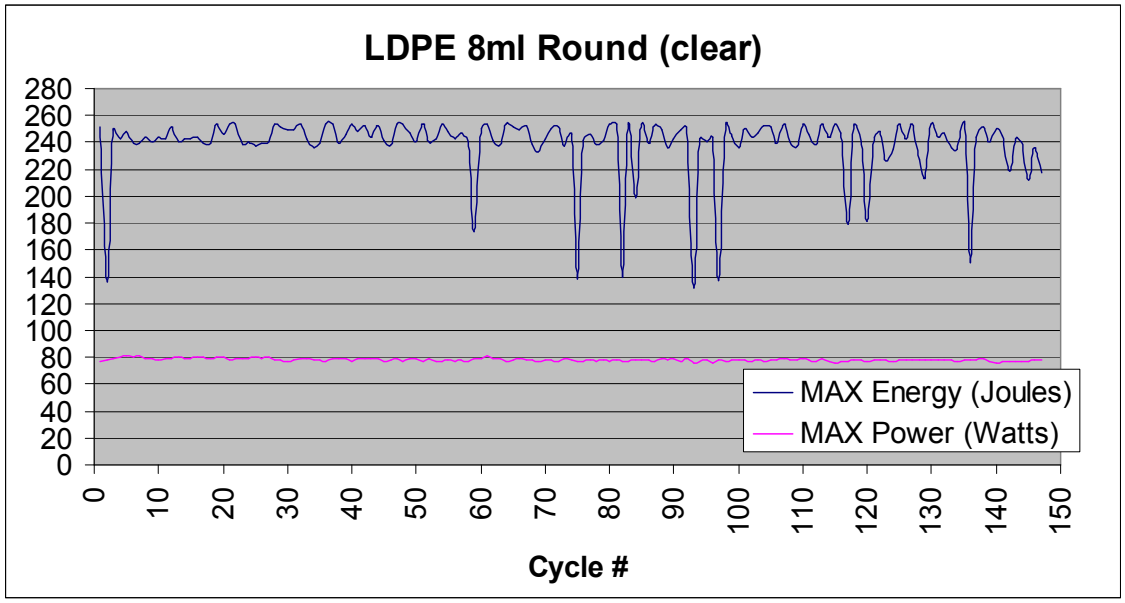


Figure 4.30 - LDPE (round) Power and Energy

4.9.3 Conclusion

The system successfully processed all bottles and materials but differences in recorded values were noted for a variety of reasons including bottle shape, bottle material, and target cutting area size and thickness. Table 4.10 compares the power and energy data collected from each test run.

Table 4.10 - Max Data Summary

LDPE (oval) MAX Data	MAX Energy (Joules)	MAX Power (Watts)
AVG	241	**114**
Min	123	94
Max	254	160
STD	26.799	20.116

LDPE (round-clear) MAX Data	MAX Energy (Joules)	MAX Power (Watts)
AVG	239	**78**
Min	132	76
Max	254	81
STD	24.415	1.026

SPP (oval-clear) MAX Data	MAX Energy (Joules)	MAX Power (Watts)
AVG	242	**118**
Min	117	92
Max	254	153
STD	25.220	18.513

PET (round-white) MAX Data	MAX Energy (Joules)	MAX Power (Watts)
AVG	238	**127**
Min	129	79
Max	254	229
STD	25.674	17.778

HDPE (round-white) MAX Data	MAX Energy (Joules)	MAX Power (Watts)
AVG	237	**84**
Min	132	83
Max	254	88
STD	25.447	0.913

Note: Raw data included in Appendix D.

Energy recorded was found to be nearly constant for each material as represented in the Figure 4.31 single cycle test result form LDPE (round). The ultrasonic generator was initiated at the start of each. There was a less than 0.04 second delay as energy was displaced linearly until the cycle is completed. Cycle start was defined as when PE1 senses a bottle in position and ended when the ultrasonic horn advances to the end of it's stroke as determined by the Hall effect switch located on the head assembly linear actuator.

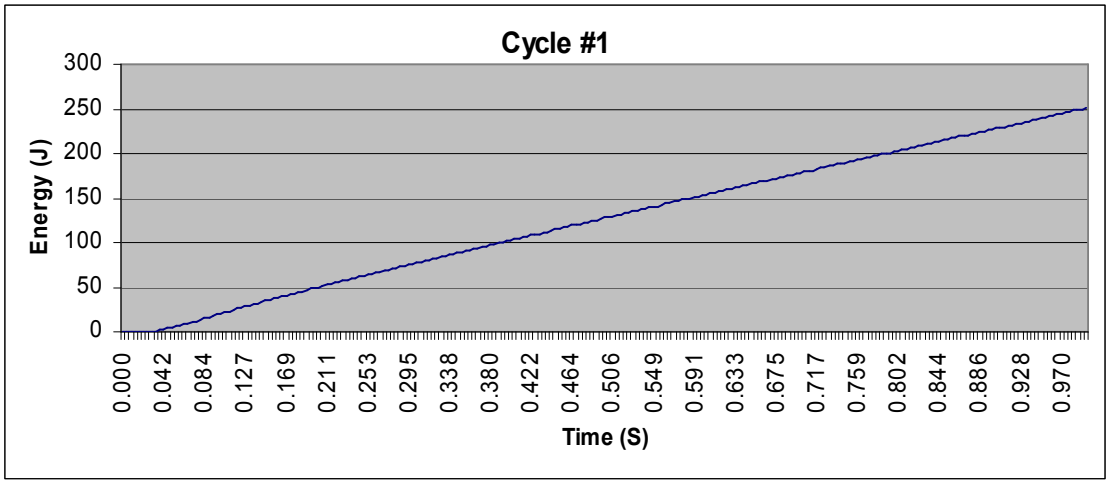


Figure 4.31 - Sample Energy Cycle

Average power displaced varied by material and physical characteristics of the cut area, i.e. diameter and wall thickness. Table 4.11 ranks the materials in order of those requiring the most power to cut to the least.

Table 4.11 – Power Comparison

Material	Bottle Cut Area		Average MAX Power (watts)	Material Properties (from Table 4.13)	
	Outside Diameter	Wall Thickness		Melting Point, deg C	Tensile Strength, Mpa
PET	1.415	0.110	**127**	243	55
SPP	0.448	0.048	**118**	130	15.2
LDPE (oval bottle)	0.448	0.048	**114**	130	14.8
HDPE	1.062	0.110	**84**	130	25.2
LDPE (round bottle)	0.506	0.077	**78**	130	14.8

Added to the table were material properties from Table 4.4. Note that these typically also decrease with the power needed to complete the cut on each bottle. The table illustrates that power therefore increases primarily with the tensile strength of the material being cut. The second parameter impacting performance to that is the diameter of the bottle cut area given the fact that the same ultrasonic was used for each cut on each bottle.

Also noted during testing, specific to the PET bottle, was the "stringy" effect during each cut. This is reflected in the melting point of PET compared with all others, 243 deg C vs. 130 deg C. Observed were strings of plastic from the bottle cut area attached to the ultrasonic horn as it traveled back and forth to its home position awaiting

the next bottle to be cut. The strings were broken as the plastic cooled when the open bottle was advanced for rotation and draining of liquid.

4.10 Operational

This next phase of testing was intended to put the Product Pooling System through production simulations equal to or greater than those expected during routine use to demonstrate that the system operates and performs as intended.

The purpose and overall objectives of operational testing were to:

- Reduce technical risk.
- Improve the system by identifying problems for resolution and/or improvement.
- Train and gain user acceptance.
- Demonstrate and document final operational performance.

The key factor is that this phase of testing is executed in a non-sterile/controlled environment with no requirements for personnel gowning. Additionally empty or water filled bottles were used for processing presenting a worst case in terms of system response. The product in any bottle adds weight and serves to stabilize the bottle as it travels through the system.

Key to the objectives above is to assure the system is truly ready to test. Operational testing was executed with scientists which have performed the manual process using a quantity of 2050 of 8ml LDPE round bottles containing 5.2g of water each. Table 4.12 summarizes data from each of two phases of the test.

Table 4.12 - Normal Operations Test, Pooled Solution Evaluation

Run Notes:	Using 8ml Bottles filled with 5.2g Sterile Water.		
	Pooled solution into two 10L glass carboys.		
Total Units Processed:	2050	Total Run Time:	7:03:43

Test Run - Phase 1

Time Intervals	delta Time (minutes)	Units at Time	Cycle Time Bottles/Minute
0:00:00	-	0	-
1:07:05	67.08	272	4.1
1:44:38	37.55	437	4.4
2:03:30	18.87	527	4.8
2:31:30	28.00	666	5.0
3:00:00	28.50	805	4.9
3:39:28	39.47	1000	4.9

10L Carboy – Pooled Solution:

Final Weight =	9815	grams
Tare Weight =	4789.4	grams
Net Weight =	5025.6	grams
Calculated g/bottle =	5.03	grams

Solution Loss (using target 5.2g fill/bottle)= 3.4%

Avg. Cycle Time = 4.7 Bottles per Minute

Test Run - Phase 2

Time Intervals	delta Time (minutes)	Units at Time	Cycle Time Bottles/Minute
0:00:00	-	0	-
0:19:00	19.00	100	5.3
0:38:00	19.00	192	4.8
1:08:30	30.50	342	4.9
1:47:10	38.67	544	5.2
2:08:00	20.83	653	5.2
3:00:00	52.00	923	5.2
3:24:15	24.42	1050	5.2

10L Carboy – Pooled Solution:

Final Weight =	9992	grams
Tare Weight =	4687	grams
Net Weight =	5305	grams
Calculated g/bottle =	5.05	grams

Solution Loss (using target 5.2g fill/bottle)= 2.8%

Avg. Cycle Time = 5.1 Bottles per Minute

This initial production simulation of the system was successfully completed with no rejected units and was further met with overwhelming enthusiasm and acceptance by scientists with experience performing the manual process as this was their first true observation of the system at work.

Testing also quantified some information never considered before for this processing and that is an issue of solution loss. Always discussed but never quantified during the manual processing was the actual efficiency of the process in terms of the solution collected vs. that remaining in the bottles disposed of. For this test, the determined value of 3.4 and 2.8% is at best an estimate as it is based on the number of bottles processed and the target 5.2g fill volume per bottle. This fill volume like all fill volume targets carries with it a +/- 3 to 5% variation.

4.11 Performance

With completion of all installation and operational testing, and most importantly, with user acceptance, research testing moves to the final phase – performance.

Testing Overview

Following is a summary of the Product Pooling System performance phase of testing. Each section is discussed by phase

Table 4.13 – Performance Research Phases

Phase	Date(s) Executed	Comments
Phase 1	Oct. 16	Air flow pattern testing and filming / static and dynamic
Phase 2	Oct. 19	Baseline static environmental testing
Phase 3	Oct. 24	Baseline Dynamic environmental testing, H_2O_2 carryover
Phase 4	Nov. 08	Static environmental testing
Phase 5	Nov. 09	Pooling round bottle/ suspension product / user training / environmental testing
Phase 6	Nov. 10	Dynamic, pooling oval bottle / environmental
Phase 7	Nov. 10, 13, 14, 15	Modifications
Phase 8	Nov. 16	Dynamic testing (repeat run after modifications')
Phase 9	Nov. 17, 18, 20	Modifications
	Nov. 21	Sterility Test #1, oval bottles, 1 x 10L carboy
Phase 10	Nov. 28	Sterility Test #2, round bottles, 2 lots, 2 x 10L carboys
Phase 11	Jan. 3/4	Sterility Test #3, round bottles, 2 lots, 2 days, 2 x 10L carboys

Phase 1 - Air Flow

The first test function completed is a verification that the PPS, now installed within the aseptic/controlled room in which it will be used, has adequate airflow around and inside the PPS, around those areas where the product is exposed to the surrounding environment and within the room itself.

A sterile fog generator was used to introduce a gentle flow of visible fog generated from a combination of sterile water for injection (WFI) and dry ice into the normal room air flow. This fog was then observed and video taped as to flow characteristics. The intent being that flow is generally unidirectional and downward, and that no turbulent air flow is observed. Critical areas, where product will be exposed, is observed with a blanket of air of covering it and flowing down, and away.

Figure 4.32 – Air Flow Patterns

Phase 2 – Baseline Environmental, Static Testing

With airflow verification successfully completed next was to challenge the sanitization of the PPS and room surfaces, and gather baseline environmental data with the Product Pooling System in this normal processing area.

This initial phase was to perform viable sampling with the PPS and room in a static state. This means the machine is off and the only activity in the room is that of the scientists completing the sampling followed by routine sanitization of the PPS.

Viable sampling was completed using two techniques. First was application of prepared RODAC sampling plates which are then tested and quantified for microbial growth. RODAC (Replicate Organism Detection And Counting) plates were prepared by microbiologists in glass Petri dishes.

A Petri dish is a shallow glass or plastic cylindrical dish that biologists use to culture cells, which can be bacterial, animal, plant, or fungus. For microbiology testing of the PPS, agar plates are used. Chemically, agar is a polymer made up of subunits of the sugar galactose. Agar polysaccharides serve as the primary structural support for the algae's cell walls. Dissolved in hot water and cooled, agar becomes gelatinous. Its chief use is as a culture medium for microbiological work. The dish is partially filled with warm liquid agar along with a particular mix of nutrients, salts and amino acids. After the agar solidifies, the dish is ready to receive a microbe-laden sample. For surface sampling the rounded surface of these RODAC plates are revealed, gently pressed to

surfaces by scientists according to the defined sampling plan, Figure 4.45 and then covered and returned to microbiology for analysis and reporting.

The second type of viable sampling was to detect and quantify air borne micro organisms from the room in which the PPS is operating. The objective is to assure that processing completed utilizing the PPS does not contaminate the room or environment.

This was accomplished using a piece of equipment which draws room air through it by producing a very controlled vacuum which pulls room air across a slowly rotating, larger diameter, plate. The RODAC plate was carefully uncovered and placed within the dome of the sampler. The plates are used for the detection and enumeration of microorganisms present in the air. Each plate slowly rotates within the sampler and gathers air samples for a preset time of 4 hours at which time the rotation is complete and it is covered, removed and replaced as needed to support the duration of the PPS processing. The completed plate was submitted for analysis by microbiology. Microbiologists incubate the plate, then count and report the any number of growth colonies.

Table 4.46 worksheet was utilized throughout the remainder of performance testing. Samples were collected at each phase of testing. Per this table and the corresponding sampling plan, Figure 4.33, each sample was collected at the conclusion of processing for the day by the scientists involved in the operation and submitted to microbiology for analysis and reporting. Reporting involved some 14 days to allow for incubation, therefore each subsequent phase of testing proceeds at risk.

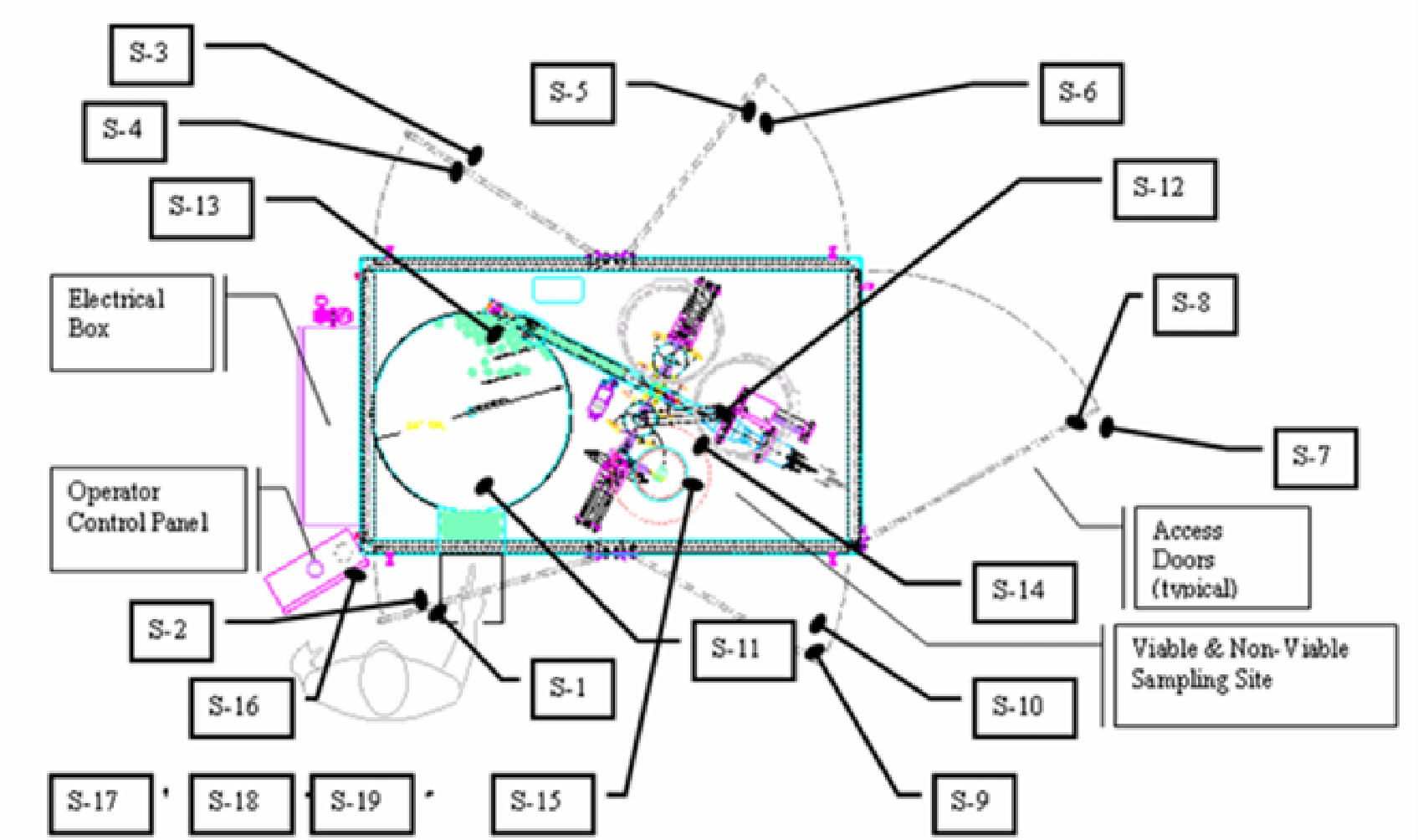


Figure 4.33 - Product Pooling System Surface Sampling Map

Table 4.14 - Environmental Sampling Worksheet Example

Seq.	Component	Result	In Spec? (Y/N)	Limit Range
1	RODAC Access Door (exterior)			0–0.1 CFU/cm^2
2	RODAC Access Door (interior)			0–0.1 CFU/cm^2
3	RODAC Access Door (exterior)			0–0.1 CFU/cm^2
4	RODAC Access Door (interior)			0–0.1 CFU/cm^2
5	RODAC Access Door (exterior)			0–0.1 CFU/cm^2
6	RODAC Access Door (interior)			0–0.1 CFU/cm^2
7	RODAC Access Door (exterior)			0–0.1 CFU/cm^2
8	RODAC Access Door (interior)			0–0.1 CFU/cm^2
9	RODAC Access Door (exterior)			0–0.1 CFU/cm^2
10	RODAC Access Door (interior)			0–0.1 CFU/cm^2
11	RODAC Rotary Infeed Table			0–0.1 CFU/cm^2
12	RODAC Top of Ultrasonic Knife			0–0.1 CFU/cm^2
13	RODAC Rotary Infeed Table			0–0.1 CFU/cm^2
14	RODAC Top of Platform			0–0.1 CFU/cm^2
15	RODAC Top of Collection carboy			0–0.1 CFU/cm^2
16	RODAC Operator Control Panel Face			0–0.1 CFU/cm^2
17	RODAC Portable Tray Cart			0–0.1 CFU/cm^2
18	RODAC Portable Vial Tray			0–0.1 CFU/cm^2
19	RODAC Portable Vial Tray			0–0.1 CFU/cm^2
20	SUM Highest CL M1 RODAC			0–0.1 CFU/cm^2
21	RODAC Room Entry Door (exterior)			0–0.1 CFU/cm^2
22	RODAC Room Entry Door (interior)			0–1.0 CFU/cm^2
23	RODAC Phone Panel			0–1.0 CFU/cm^2
24	RODAC Wall			0–1.0 CFU/cm^2
25	SUM Highest CL M1 RODAC			0–1.0 CFU/cm^2
26	RODAC floor Surface			0–1.0 CFU/cm^2

Testing is rigorous as viable samples were incubated for a total of 14 days, 7 of which are at 20-25 deg C and 7 consecutive, additional days at an elevated temperature, thus promoting growth, of 30-35 deg C.

Results from the initial phase of environmental viable testing were critical as, at this point, any failure initiates a step back for corrective action and repeat testing. This was the first in a series of milestone events during this performance phase. Initial, successful, static testing results are shown in Table 4.15.

Table 4.15 - Phase 2 Baseline Static, Environmental Testing Results

Seq.	Component	Result	Units	In Spec? (Y/N)
1	RODAC Access Door (exterior)	0.0	CFU/cm^2	Y
2	RODAC Access Door (interior)	0.0	CFU/cm^2	Y
3	RODAC Access Door (exterior)	0.0	CFU/cm^2	Y
4	RODAC Access Door (interior)	0.0	CFU/cm^2	Y
5	RODAC Access Door (exterior)	0.0	CFU/cm^2	Y
6	RODAC Access Door (interior)	0.0	CFU/cm^2	Y
7	RODAC Access Door (exterior)	0.0	CFU/cm^2	Y
8	RODAC Access Door (interior)	0.0	CFU/cm^2	Y
9	RODAC Access Door (exterior)	0.0	CFU/cm^2	Y
10	RODAC Access Door (interior)	0.0	CFU/cm^2	Y
11	RODAC Rotary Infeed Table	0.0	CFU/cm^2	Y
12	RODAC Top of Ultrasonic Knife	0.0	CFU/cm^2	Y
13	RODAC Rotary Infeed Table	0.0	CFU/cm^2	Y
14	RODAC Top of Platform	0.0	CFU/cm^2	Y
15	RODAC Top of Collection carboy	0.0	CFU/cm^2	Y
16	RODAC Operator Control Panel Face	0.0	CFU/cm^2	Y
17	RODAC Portable Tray Cart	0.0	CFU/cm^2	Y
18	RODAC Portable Vial Tray	0.0	CFU/cm^2	Y
19	RODAC Portable Vial Tray	0.0	CFU/cm^2	Y
20	SUM Highest CL M1 RODAC	0.0	CFU/cm^2	Y
21	RODAC Room Entry Door (exterior)	0.0	CFU/cm^2	Y
22	RODAC Room Entry Door (interior)	0.0	CFU/cm^2	Y
23	RODAC Phone Panel	0.0	CFU/cm^2	Y
24	RODAC Wall	0.0	CFU/cm^2	Y
25	SUM Highest CL M1 RODAC	0.0	CFU/cm^2	Y
26	RODAC floor Surface	0.0	CFU/cm^2	Y

Phase 3 – Baseline Environmental Testing

Phase 3 of testing involved two challenges; first was research of the actual pooled solution for the carry over of sanitization solution and second was for baseline processing, termed dynamic testing, of HDPE round (water filled) bottles.

This second test was to challenge, on a preliminary basis, the full operation of the PPS under sterile or aseptic conditions, processing bottles and pooling solution while collecting what will be normal production data to assure all was within acceptable, passing, limits.

Solution Evaluation for Carryover

The objective of this first test was to functionally simulate a production operation within the controlled environment after the PPS and room had been fully and normally sanitized.

For clarification, a sanitization procedure for a aseptic processing environment involves fully gowned personnel (no exposed skin), wearing air respirators, pressure spraying a concentrated solution consisting of paracetic acid and, primarily, hydrogen peroxide on all surfaces within the target environment. This includes the PPS. Following this sanitization a routine secondary process of manually wiping PPS surfaces with a isopropyl alcohol and sterile water solution was completed.

Never challenged for the manual process, this phase of research involved processing bottles filled with sterile water, pooling this water, then submitting the solution for analysis of contained peroxide. Any carry-over of sanitization into the

pooled solution at detection levels above 1 ppm would lead to redesign and/or seeking different methodology for sanitization. The current procedure described is already a well established, tried and proven, and validated method.

PPS operation was completed normally, processing 1800 bottles and pooling 13Kg of solution within the prepared, sterilized, glass 20L carboy. The glass carboy was sealed and safely, being cautious of the total weight of the liquid filled glass carboy, submitted to analytical chemistry for evaluation and reporting of results.

The very welcomed and successful results provided are represented in Figure 4.34. All result well under the 1ppm limit.

Sample Text : *STANDARD*
Test for total peroxides of residual Spor-Klenz solution as previously tested in LN11139:017-019.

Result Information

Task ID	Component	Result Value	Units	Rep
301223718	COMPONENT ASSAYED	PEROXIDE		1
301223718	CONCENTRATION	0.23	ppm	1
301223718	MINIMUM DETECTION LIMIT	NOT DONE	ppm	1
301223718	COMPONENT ASSAYED	PEROXIDE		2
301223718	CONCENTRATION	0.26	ppm	2
301223718	MINIMUM DETECTION LIMIT	NOT DONE	ppm	2

Average of two aliquots taken from the same container = 0.24 ppm.

Task Information

Task ID	Method	Procedure	Method Datagroup	Condition
301223718	RINSE SOLUTION ANALYSIS	PROCEDURE IN DEVELOPMENT	AC(CHEMICAL)	APPROVED

Result Information

Task ID	Component	Result Value	Units	Rep
301223716	COMPONENT ASSAYED	PEROXIDE		1
301223716	CONCENTRATION	0.61	ppm	1
301223716	MINIMUM DETECTION LIMIT	NOT DONE	ppm	1
301223716	COMPONENT ASSAYED	PEROXIDE		2
301223716	CONCENTRATION	0.55	ppm	2
301223716	MINIMUM DETECTION LIMIT	NOT DONE	ppm	2

Average of two aliquots taken from the same container = 0.58 ppm.

Task Information

Task ID	Method	Procedure	Method Datagroup	Condition
301223716	RINSE SOLUTION ANALYSIS	PROCEDURE IN DEVELOPMENT	AC(CHEMICAL)	APPROVED

Figure 4.34 – Pooled Solution Carryover Test Results

Baseline Processing

With this previous criteria successfully met the process started of gradually increasing the research challenges and associated difficulty in terms of both criteria and testing.

This next phase was termed dynamic testing which added the great source of contamination, people. The baseline dynamic test was completed using water filled 8ml

round (LDPE) bottles. The test was executed by just myself, completing the processing of 1800 bottles in 6 hours and 15 minutes. Viable sampling, testing and analysis was completed following the run with results shown in Table 4.16.

Table 4.16 - Phase 3 Baseline Dynamic, Environmental Testing Results

Seq.	Component	Result	Units	In Spec? (Y/N)
1	RODAC Access Door (exterior)	0.0	CFU/cm^2	Y
2	RODAC Access Door (interior)	0.0	CFU/cm^2	Y
3	RODAC Access Door (exterior)	0.0	CFU/cm^2	Y
4	RODAC Access Door (interior)	0.0	CFU/cm^2	Y
5	RODAC Access Door (exterior)	0.0	CFU/cm^2	Y
6	RODAC Access Door (interior)	0.0	CFU/cm^2	Y
7	RODAC Access Door (exterior)	0.0	CFU/cm^2	Y
8	RODAC Access Door (interior)	0.0	CFU/cm^2	Y
9	RODAC Access Door (exterior)	0.0	CFU/cm^2	Y
10	RODAC Access Door (interior)	0.0	CFU/cm^2	Y
11	RODAC Rotary Infeed Table	0.0	CFU/cm^2	Y
12	RODAC Top of Ultrasonic Knife	0.0	CFU/cm^2	Y
13	RODAC Rotary Infeed Table	0.0	CFU/cm^2	Y
14	RODAC Top of Platform	0.0	CFU/cm^2	Y
15	RODAC Top of Collection carboy	0.0	CFU/cm^2	Y
16	RODAC Operator Control Panel Face	0.0	CFU/cm^2	Y
17	RODAC Portable Tray Cart	0.0	CFU/cm^2	Y
18	RODAC Portable Vial Tray	0.0	CFU/cm^2	Y
19	RODAC Portable Vial Tray	0.0	CFU/cm^2	Y
20	SUM Highest CL M1 RODAC	0.0	CFU/cm^2	Y
21	RODAC Room Entry Door (exterior)	0.0	CFU/cm^2	Y
22	RODAC Room Entry Door (interior)	0.0	CFU/cm^2	Y
23	RODAC Phone Panel	0.0	CFU/cm^2	Y
24	RODAC Wall	0.0	CFU/cm^2	Y
25	SUM Highest CL M1 RODAC	0.0	CFU/cm^2	Y
26	RODAC floor Surface	0.0	CFU/cm^2	Y

Phase 4 – Environmental, Static Testing

Phase 4 became the "official" first environmental test, fully documented. It included all testing described in Phase 2. In addition, Phase 4 added non-viable particulate counting in two particle sizes, 0.5 micron and 5.0 micron, during testing. Also new in this phase was data collection and trending of the environment for differential pressure, relative humidity and temperature, and personnel monitoring for microbial contamination.

Non-Viable Particulate Monitoring

Recorded and analyzed data for this static environmental phase are displayed in Figures 4.35 and 4.36. The figures show the accumulated number of counts totaling both 0.5 micron size particulates and 5.0 micron size particulates over the time of test. Observed, is that during personnel activity sanitizing within the PPS and moving around the room particle counts increase for both sizes but in particular for the smaller 0.5 micron size.

This comes as no surprise as sanitizing solution is sprayed onto various surfaces followed by a wipe down procedure after sufficient contact time had passed. Also initial sanitization is performed using a paracetic acid/hydrogen peroxide solution. This is then followed by a isopropyl alcohol/sterile water wipe down.

Table 4.17 defines the allowable limits for particle counts for each size and it is noted that results were well below allowable limits as expected for this static test.

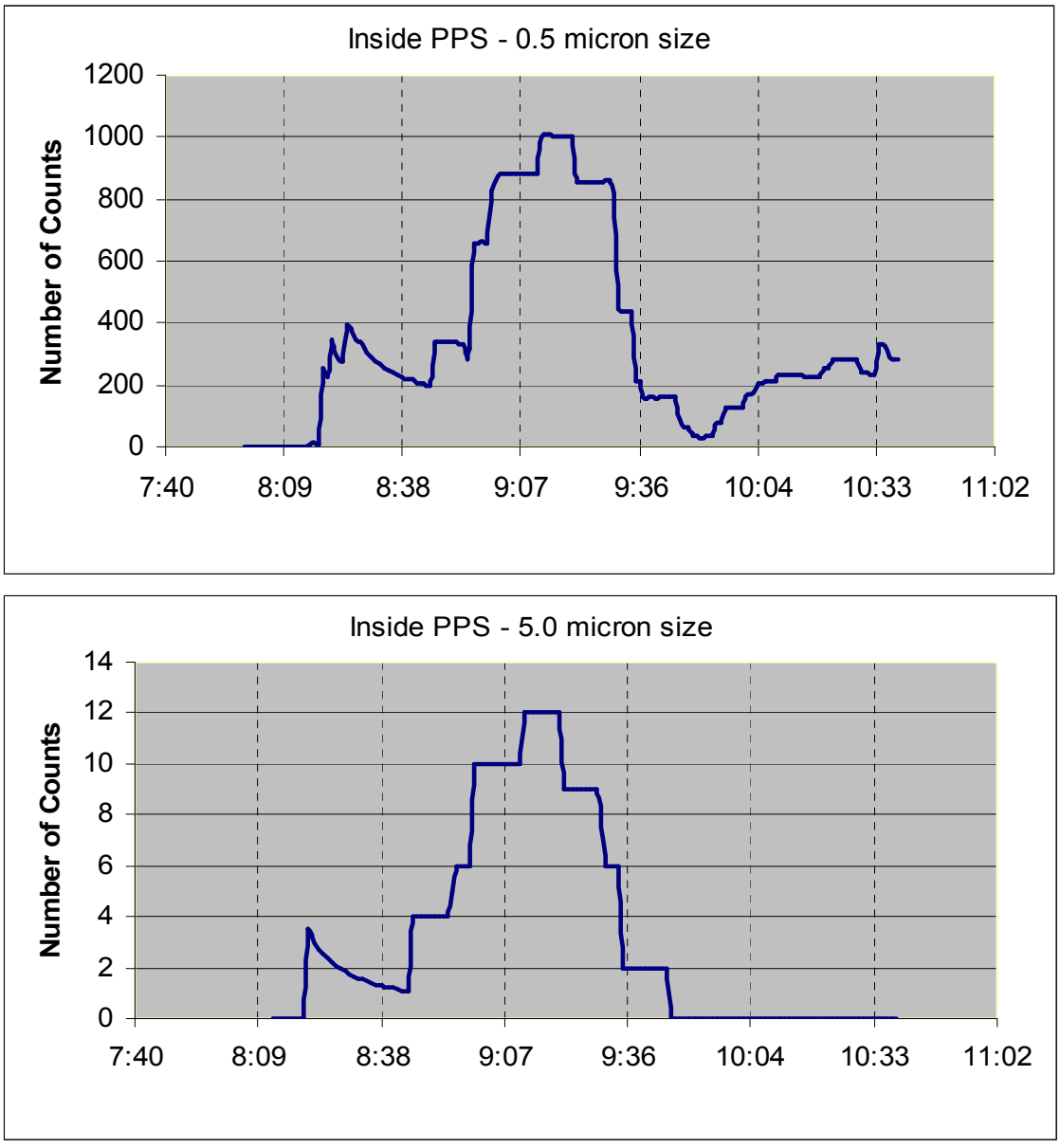
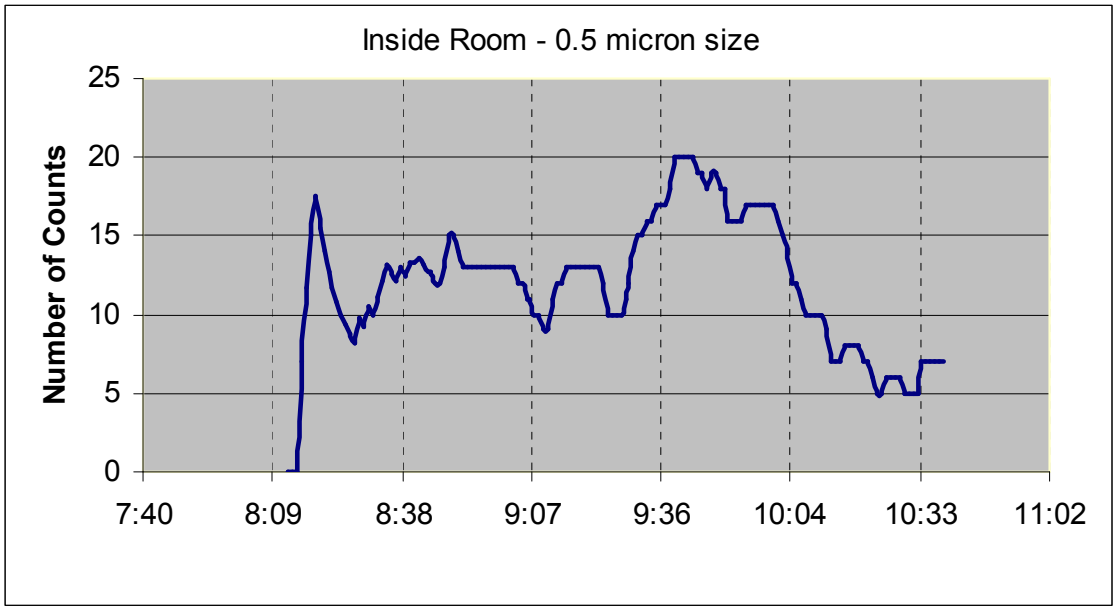


Figure 4.35 – PPS Non-Viable Particulates, Phase 4 Static Env. Test



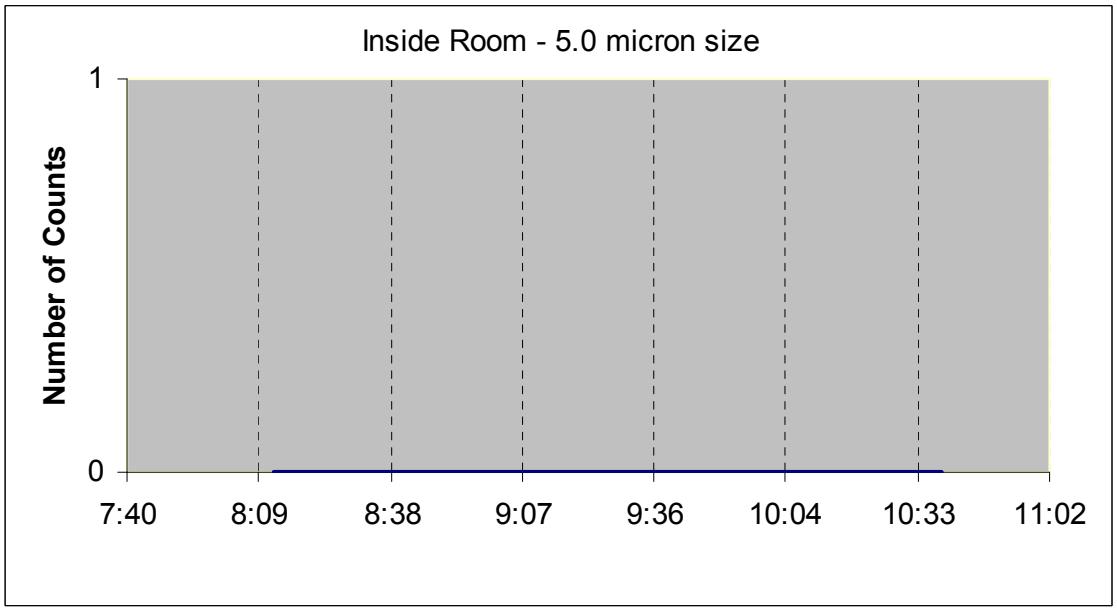


Figure 4.36 – Room Non-viable Particulates, Phase 4 Static Env. Test

Table 4.17 - Environmental Limits

Parameter	Units	Minimum	Maximum
0.5 particle size	Number of counts	n/a	3,520 per cubic meter of air sampled
5.0 particle size	Number of counts	n/a	29 per cubic meter of air sampled
Temperature	Deg F	55	65
Relative Humidity	%	n/a	60
Differential Pressure	Inches WC	0.05	n/a

Environmental Monitoring

The above Table 4.17 also defines limits for room temperature, relative humidity and differential pressure. These are each critical parameters which were monitored and trended during processing to assure that the PPS, and all that is involved in utilizing it for aseptic processing, does not adversely effect the environment. These limits are set by regulatory agencies for aseptic processing including Food and Drug Administration (FDA) and, internationally, the International Standards Organization (ISO).

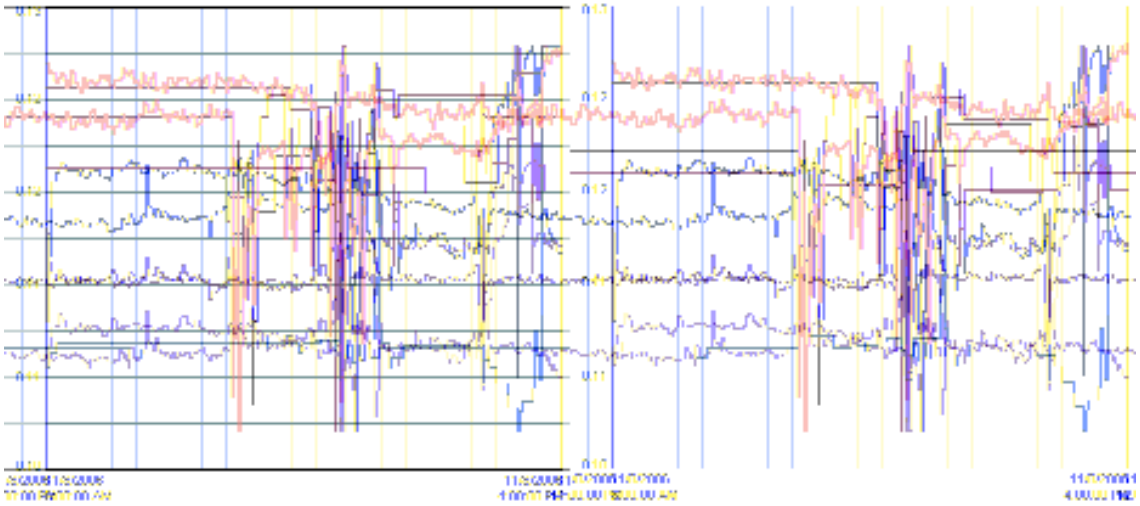


Figure 4.37 Differential Pressure Trend, Phase 4

Figure 4.37 lustrates that differential pressure values continuously stayed above 0.05 inches of water column as measured from the fill room to outside connecting corridor. All areas were trended during this phase of testing to confirm that no area was adversely affected. The table below shows the trend color legend and minimum and maximum values for the processing period.

TagName	N..	V..	S	Description	Color	Minimum	Maximum
URM124-146_DIFF_PRESS	1	☑	U	ROOM 124-146 DIFF PRESSURE SIGNAL		0.08	0.09
URM125-146_DIFF_PRESS	2	☑	U	ROOM 125-146 DIFF PRESSURE SIGNAL		0.10	0.15
URM126-146_DIFF_PRESS	**3**	☑	**U**	**ROOM 126-146 DIFF PRESSURE SIGNAL**		**0.10**	**0.13**
URM127-123_DIFF_PRESS	4	☑	U	ROOM 127-123 DIFF PRESS SIGNAL		0.06	0.10
URM128-127_DIFF_PRESS	5	☑	U	ROOM 128-127 DIFF PRESSURE SIGNAL		0.05	0.08
URM146-128_DIFF_PRESS	6	☑	U	ROOM 146-128 DIFF PRESSURE SIGNAL		0.06	0.10
URM146-129_DIFF_PRESS	7	☑	U	ROOM 146-129 DIFF PRESSURE SIGNAL		0.13	0.16
URM146-142_DIFF_PRESS	8	☑	U	ROOM 146-142 DIFF PRESSURE SIGNAL		0.16	0.25

The data trend for relative humidity, Figure 4.38 also shows values below the 60% RH upper limit. Trend does increase as the environment is populated with "people" heat during sanitization and sampling.

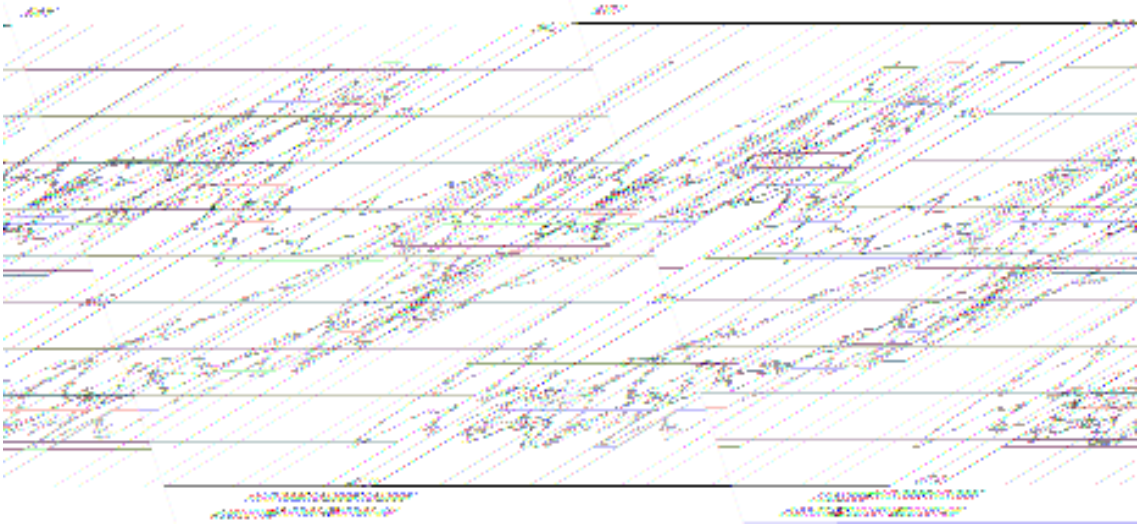


Figure 4.38 - Relative Humidity Trend – Phase 4

All areas were trended during this phase of testing for relative humidity to confirm that no area was adversely affected. The table below shows the trend color legend and minimum and maximum values for the processing period.

TagName	N..	V..	S	Description	Color	Minimum	Maximum	Units
URM124_HUMIDITY	**2**	☑	**U**	**ROOM 124 HUMIDITY SIGNAL**		**47.9**	**54.2**	**%RH**
URM125_HUMIDITY	3	☑	U	ROOM 125 HUMIDITY SIGNAL		51.2	58.1	%RH
URM126_HUMIDITY	4	☑	U	ROOM 126 HUMIDITY SIGNAL		51.6	56.4	%RH
URM127_HUMIDITY	5	☑	U	ROOM 127 HUMIDITY SIGNAL		52.4	54.1	%RH
URM128_HUMIDITY	6	☑	U	ROOM 128 HUMIDITY SIGNAL		51.4	54.1	%RH
URM129_HUMIDITY	7	☑	U	ROOM 129 HUMIDITY SIGNAL		52.0	53.8	%RH
URM146_HUMIDITY	8	☑	U	ROOM 146 HUMIDITY SIGNAL		52.1	54.7	%RH

Figure 4.39 data trend illustrates that area temperature values also continuously stayed within the desired range of 55 to 65 deg F during processing.

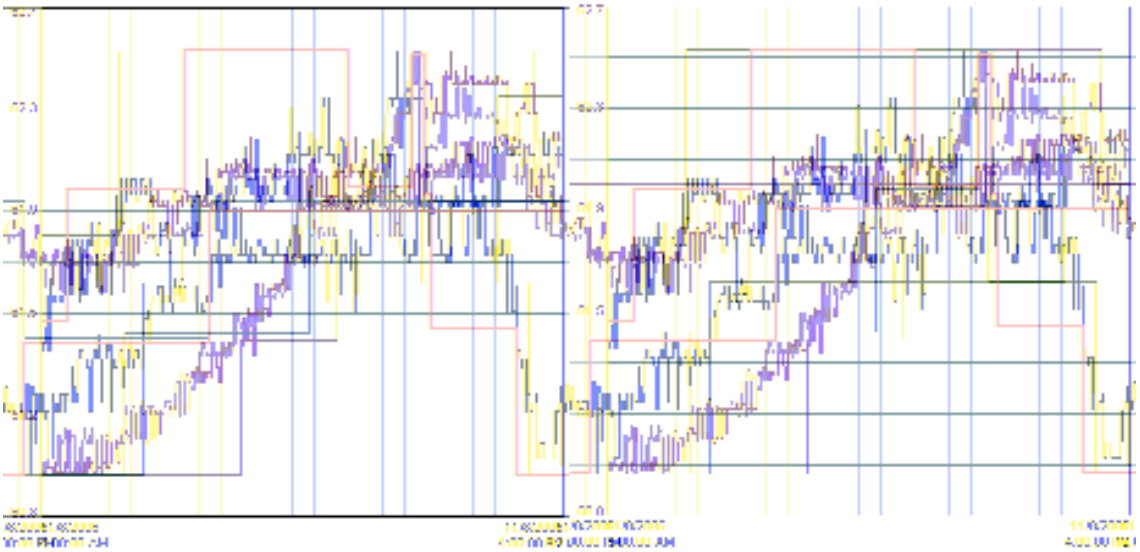


Figure 4.39 - Temperature Trend, Phase 4

All areas were trended for temperature during this phase of testing to confirm that no area was adversely affected. The table below shows the trend color legend and minimum and maximum values for the processing period.

TagName	N..	V..	S	Description	Color	Minimum	Maximum	Units
URM124_TEMP	**2**	☑	**U**	**ROOM 124 TEMPERATURE SIGNAL**		**60.8**	**62.7**	**DEC C**
URM125_TEMP	3	☑	U	ROOM 125 TEMPERATURE SIGNAL		60.7	62.2	°F
URM126_TEMP	4	☑	U	ROOM 126 TEMPERATURE SIGNAL		59.8	61.0	%RH
URM127_TEMP	5	☑	U	ROOM 127 TEMPERATURE SIGNAL		59.3	61.2	°F
URM128_TEMP	6	☑	U	ROOM 128 TEMPERATURE SIGNAL		59.7	61.8	°F
URM129_TEMP	7	☑	U	ROOM 129 TEMPERATURE SIGNAL		59.8	61.9	°F
URM146_TEMP	8	☑	U	ROOM 146 TEMPERATURE SIGNAL		62.6	64.5	°F

Personnel Monitoring

Added to the PPS and room testing was personnel testing. As noted earlier, people are the greatest risk to the environment and to any pooled product. Scientists and

engineers both go through a gowning process as they enter increasingly tighter controlled environments.

For example, starting from an uncontrolled environment, one removes all jewelry, makeup (as applicable) and dons dedicated uniform and shoes. Just before entering the least controlled area, the pre-gown room, one dons hair cover, face cover (as applicable) and shoe covers. Entering through the pre-gown room and into the gown room, which is one level up on the controlled area ladder, you begin the gowning process.

The gowning process involves a unique step wise approach, first gathering needed pre-sterilized, double packaged components in your correct size from the storage cabinet; two pair of nylon gloves, head cover, face cover, body suit, boot covers and goggles. One pair of gloves goes on first, followed by the head cover, then the face cover, next without any part touching the floor, don the body suit, then without leaning or sitting, lift one foot, don one boot cover and step into the designated cleaner environment, lift the second foot into the air, don the second boot cover. Place on the second pair of nylon gloves and finally don the sterile goggles. Clean hands with sterilizing solution and enter the next highest level of controlled area, the sterile corridor. From the corridor, one enters the sterile or aseptic fill room in which the PPS resides.

Moving forward from this point through the various phases of testing, personnel testing was included. After each phase of testing viable sampling and

analyses was conducted on each participating scientist or engineer. These dynamic tests are the ultimate in testing all involved components of the process; people, area, environment, support systems, components to be processed, PPS machine and product.

I cannot over emphasize that any single failure, among so many opportunities, in any phase of research at this point and forward, constitutes an investigation as to cause, corrective action and extensive repeat execution of testing.

Personnel results associated with the first dynamic test are illustrated in Table 4.18. This testing was rigorous as viable samples are incubated for a total of 14 days, 7 of which at 20-25 deg C and 7 consecutive, additional days at an elevated temperature, thus promoting growth, of 30-35 deg C.

Table 4.18 - Phase 4, Dynamic #1, Personnel Testing Results

RODAC				
Sample Site	Colonies per 25 cm^2			CFU/cm^2
	Bacterial	Fungal	Total	
Body - chest	0	0	0	0
Body - forearm	0	0	0	0
Body - palm	0	0	0	0
Touchplate				
Sample Site	Colonies per Plate			CFU/Plate
	Bacterial	Fungal	Total	
Fingers, Left & Right	0	0	0	0

Phase 4 Conclusion

This phase of research was successfully completed with gained knowledge and documentation that the PPS met the static environmental challenges. It included all testing described in Phase 2. In addition, Phase 4 added non-viable particulate counts in two particle sizes, 0.5 micron and 5.0 micron during testing. Also new in this phase was successful data collection and trending of the environment for differential pressure, relative humidity and temperature, and personnel monitoring for microbial contamination.

Phase 5 – Environmental, Dynamic Testing 1 of 2

Phase 5 and 6 involved dynamic testing. Objectives of dynamic testing include; user training, environmental data collection and "continuous improvement" of the PPS.

Phase 5 specifically involved user training and the additional challenge of processing a unique product sample while evaluating all of the corresponding environmental data.

It was expected that as far as scientist manipulation and interaction with the PPS was concerned, that this product would be a worst-case scenario.

The product processed was contained in 10ml LDPE round bottles. About 1000 were available and each contained a "suspension" product. This type of product required the scientist to individually place each bottle on a small electric vibratory table for about 10 seconds each. The scientist visually observed the product dissolve into a

homogeneous solution and then, one by one, placed the bottle on the rotary infeed table of the PPS.

The bottle was then carried through the PPS as usual and processed with the solution pooled into a prepared sterile glass 10L carboy. An added challenge was to retain samples of the individual product bottles and compare this product to the pooled product therefore challenge the PPS to process the bottles in a timely manner and to pool all of the contained active ingredients in each bottle. Simply, does the pooled solution equal the starting solution.

During this process of handling each bottle, environmental data was trended. Figure 4.40 shows the differential pressure data for the processing period. Note the peaks and valleys due to handling but all values stay well above the minimum of 0.05 inches water column.

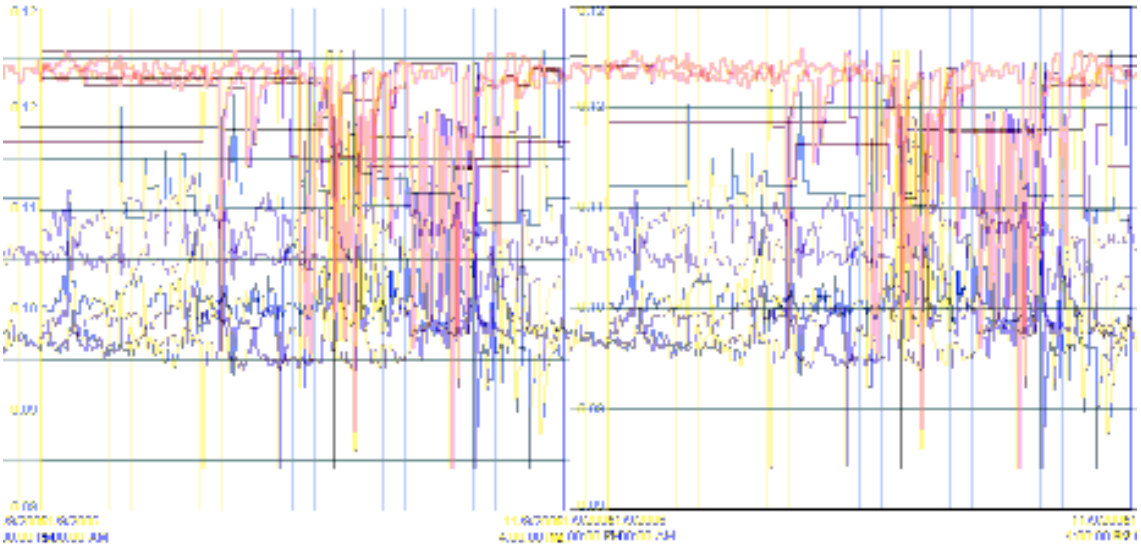


Figure 4.40 - Differential Pressure Trend, Phase 5

The data trend for relative humidity, Figure 4.41, shows values below the 60% RH upper limit. Trend again does increase as the environment is populated with "people" and activity.

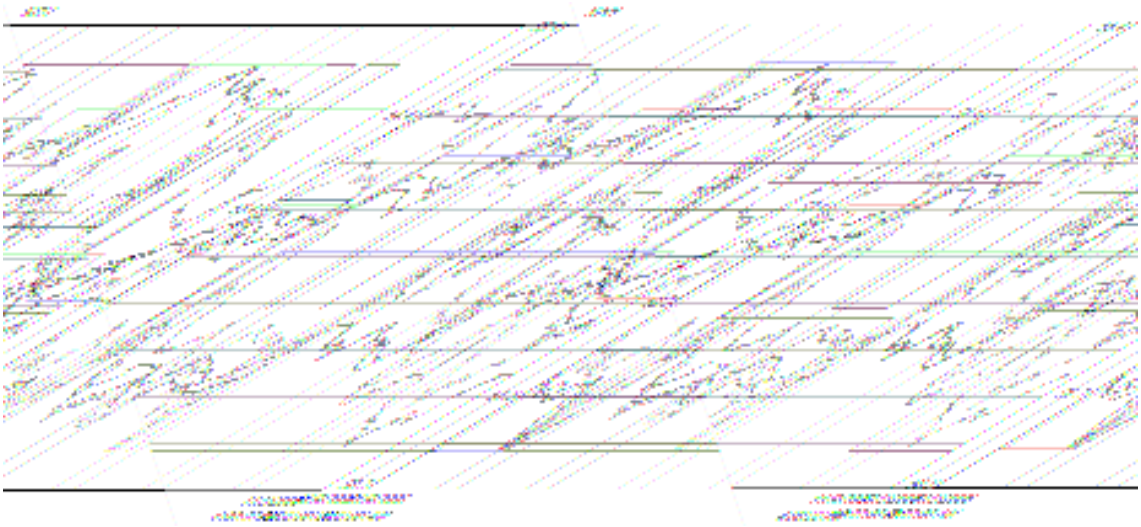


Figure 4.41 - Relative Humidity Trend, Phase 5

Figure 4.42 data trend illustrates that area temperature values also continuously stayed within the desired range of 55 to 65 deg F during processing.

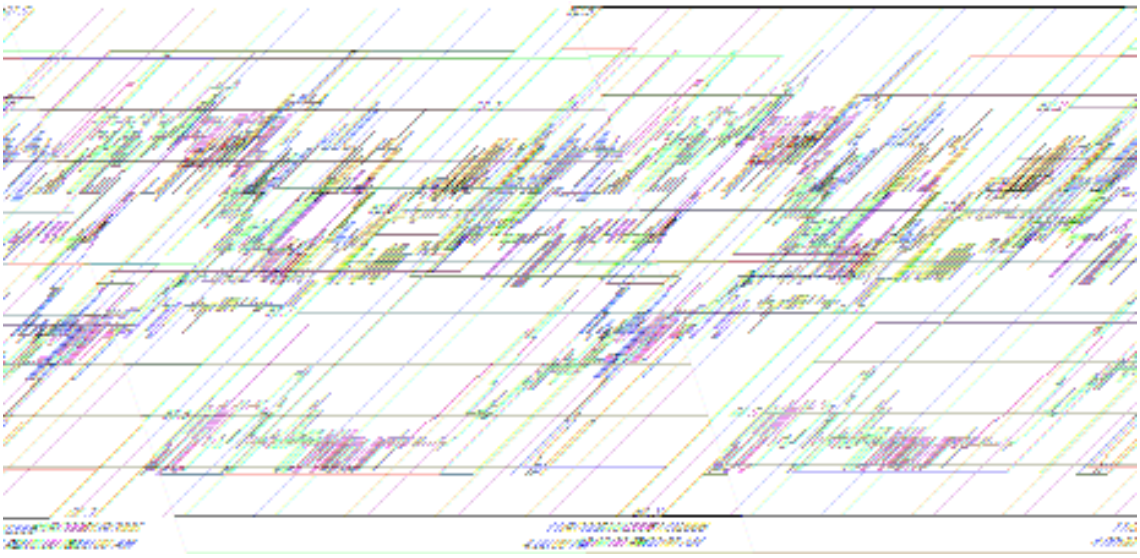


Figure 4.42 - Temperature Trend, Phase 5

Phase 5 Conclusion

This research phase was successfully completed and documented results for user training, environmental data collection and "continuous improvement" of the PPS.

Phase 5 specifically involved user training and the additional challenge of processing a unique product sample while evaluating all of the corresponding environmental data. It was expected that as far as scientist manipulation and interaction with the PPS was concerned, that this product represented a worst-case scenario.

Additionally, this phase competed the evaluation of pooled solution to starting solution. No difference was found by analytical chemistry.

Phase 6 – Environmental, Dynamic Testing 2 of 2

Phase 6, the second of the two dynamic tests, challenged yet another product, the processing of small oval bottles. Oval bottles, especially the 4mL size, are notoriously unstable for automated processing. The capped bottles are top heavy with a high center of gravity and little base support with their thin oval shaped base. They waddle like penguins and easily fall over.

As mentioned, an objective of dynamic testing was to put forth challenges in terms of products to be processed. The processing of oval bottles certainly afforded the opportunity to observe scientists operate the PPS and observe any opportunities for improvements. All processing was successfully completed but with difficulty.

Figures 4.43 through 45 illustrate that all differential pressures, relative humidity's and temperatures stayed within operating limits throughout processing.

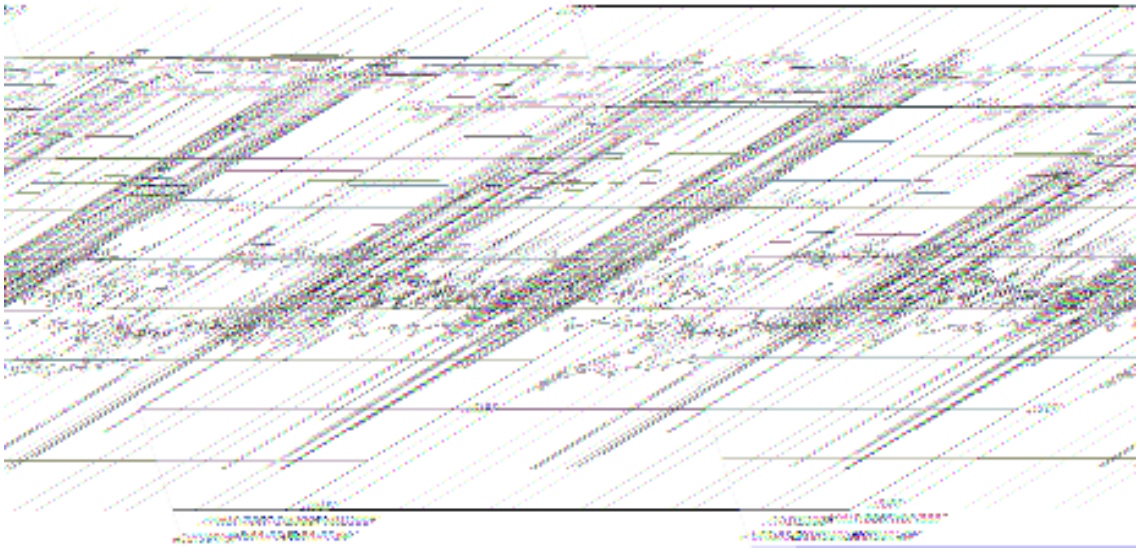


Figure 4.43 - Differential Pressure Trend – Phase 6

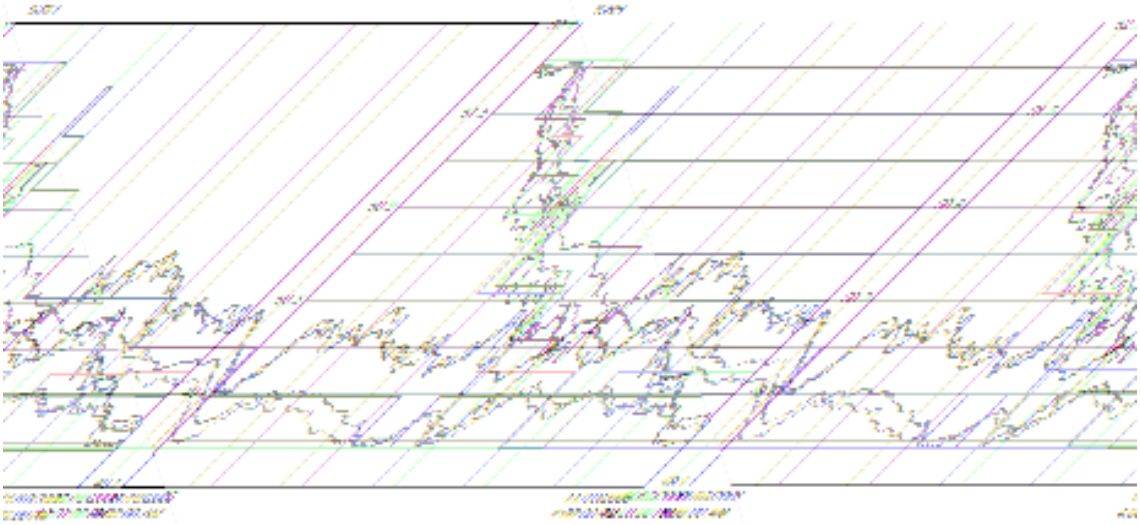


Figure 4.44 - Relative Humidity Trend, Phase 6

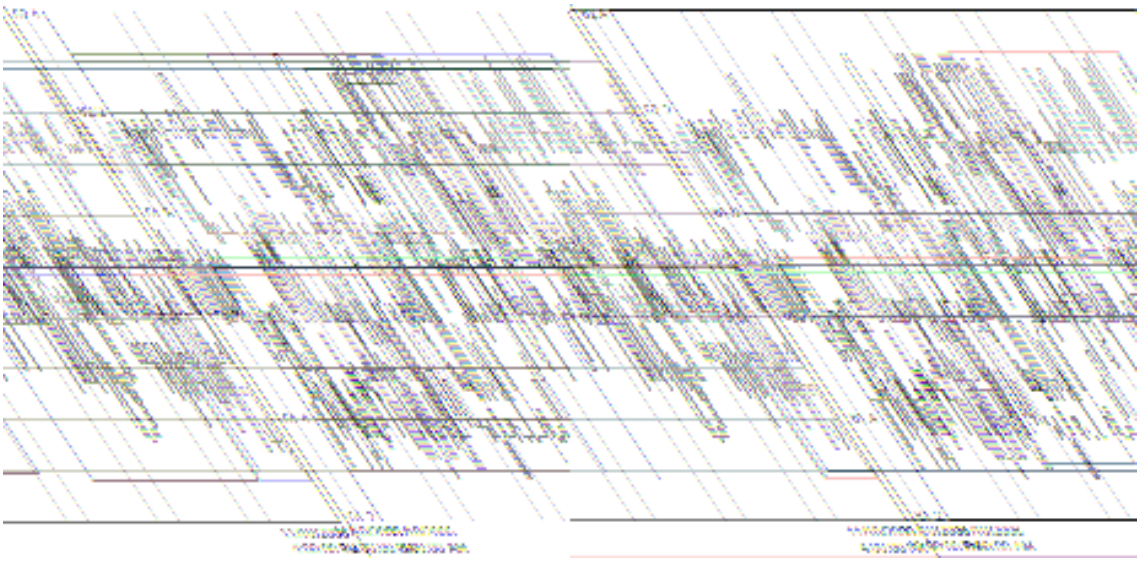


Figure 4.45 - Temperature Trend, Phase 6

Phase 6 Conclusion

Good news-bad news. All 1200 bottles were processed successfully but I added a pause as I identified needed modifications in this research, a pause defined as Phase 7.

Phase 7 – Modifications

Nothing teaches like experience therefore as I was gowned from head to toe within the aseptic area witnessing processing of the second dynamic run I immediately began to note areas for improvement.

Quickly engineered and fabricated were;

1. A new flat bottle guide rail to replace the round bar version, this new flat bar guide provides lower support and stability to the bottles on the right side as they travel down the infeed conveyor.
2. Two new bottle grippers such that the bottles may be ripped at a lower, closer to the bottom, position. Especially important for the oval bottles due to their shape.
3. Modification of the singulator fingers to increase the angle at which the engage and disengage the bottles as they are held, staged, and individually released to the ultrasonic cutting station. Also added were polyethylene extensions to make the fingers effectively wider or thicker to offer stability to the bottles held on top of a moving conveyor.
4. Modification of the ultrasonic cutting angle to create about 2 degree upward cutting angle vs. the previous horizontal cutting angle. This compensates for

bottle deflection and reduces the force during cutting as before the bottle was being slightly compressed against the conveyor but the top is now observed as being lifted as the cut travels through the bottle.

5. An observation noted during emptying the oval bottles is one of "speed kills". Observed were the open top bottles being inverted so fast that enough air was not being drawn into the bottle to allow the contained liquid to drain out through the 3-4mm cut opening. The liquid filled bottles were being inverted and up righted, and then disposed off while still containing the liquid. This blanking effect was corrected by using the "engineered in" pneumatic flow controls for the inversion motion. The forward, draining, rotation was drastically slowed down so that the liquid draining could initiate before the opening was blanked off with liquid. The return or up righting motion was then drastically accelerated so as not to lose any overall cycle time.
6. Added was a flow control to the return movement for the ultrasonic horn. This addition allowed for the controlled return of the horn to its home position.
7. Control system, PLC programming, changes were to remove the requirement for the cycle to proceed at the bottle gripper station when PE1 is initially made. With the conveyor movement this photo eye would at times make and break causing the cycle to stall. A timer was added to the logic such that when the eye is made a 0.2 second delay timer initiates and the cycle proceeds not matter whether or not the eye makes or breaks again.

With these changes, implemented and tested, Phase 7 comes to an end.

Phase 8 – Dynamic Testing Repeated

With the modifications completed, a third run of dynamic testing was executed. As in phase 6, once again small 4mL oval bottles are the customers but this time instead of a translucent LDPE bottle, this product is packaged in white SPP bottles. 651 bottles were successfully processed and solution pooled in order to demonstrate the modifications to my customers, the users.

Figures 4.46 through 50 illustrate that collected and trended data for all differential pressures, relative humidity's and temperatures stayed within operating limits throughout processing.

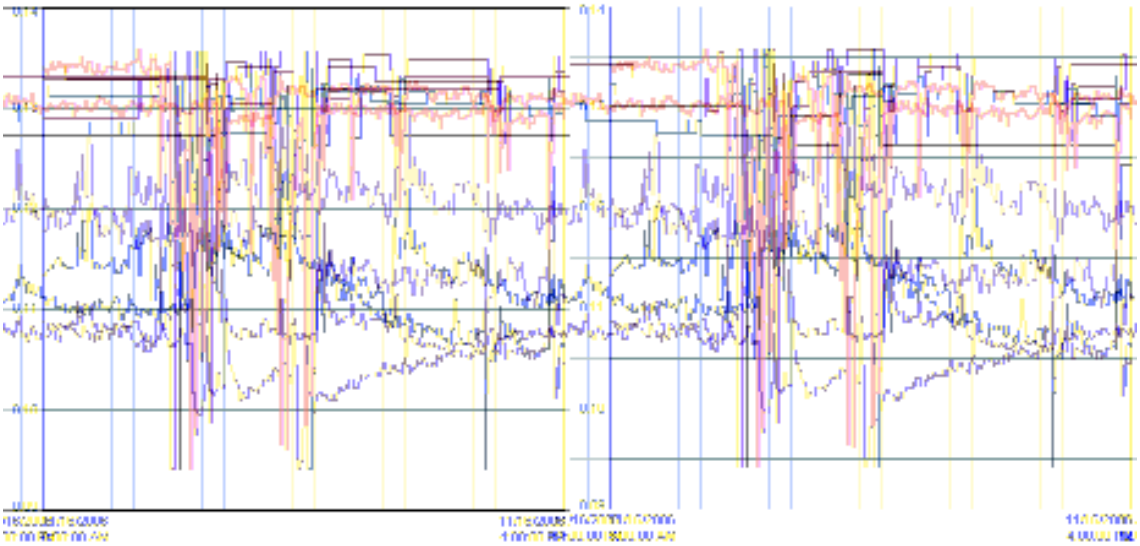


Figure 4.46 - Differential Pressure Trend, Phase 8

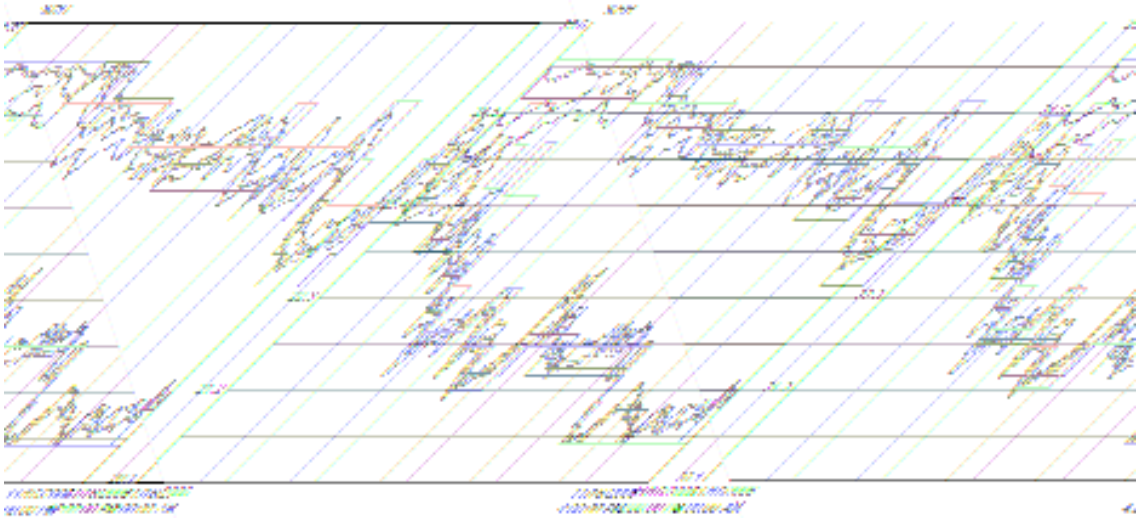


Figure 4.47 - Relative Humidity Trend, Phase 8

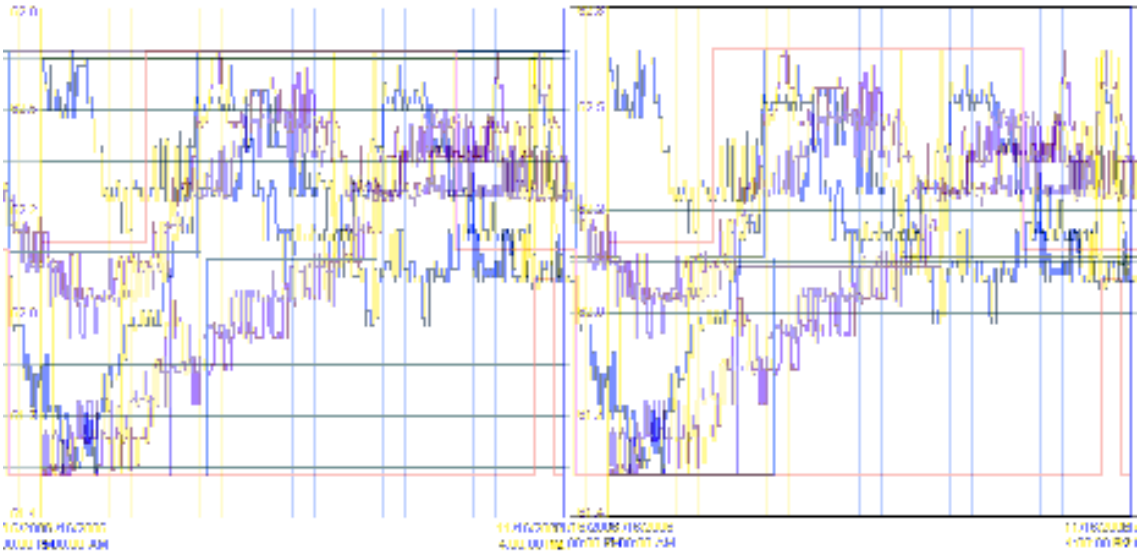


Figure 4.48 - Temperature Trend, Phase 8

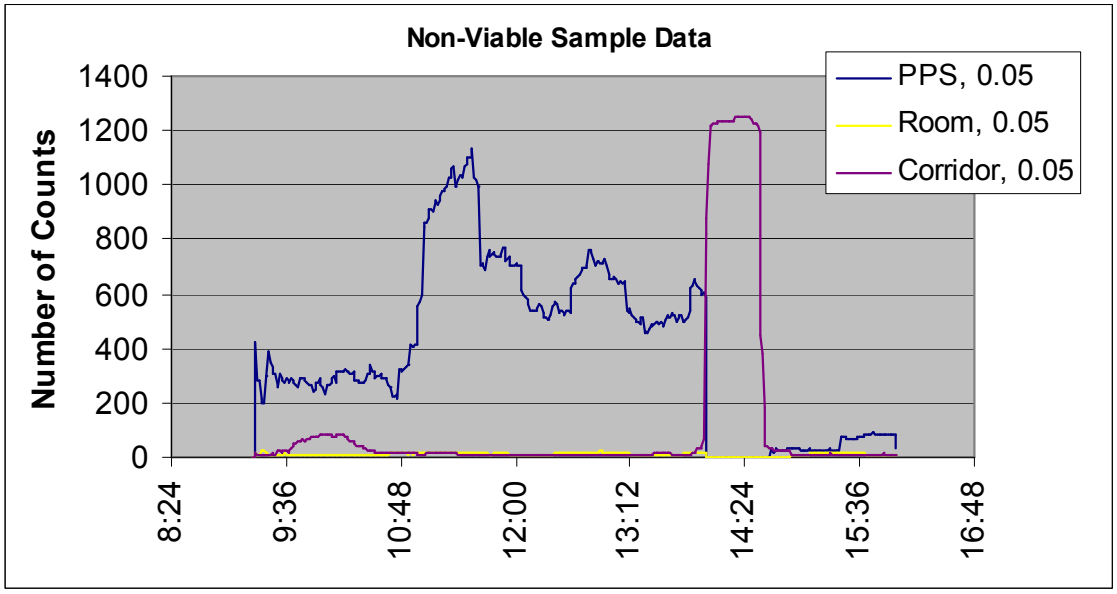


Figure 4.49 - Non-viable Particulate Trend, 0.05 micron Trend, Phase 8

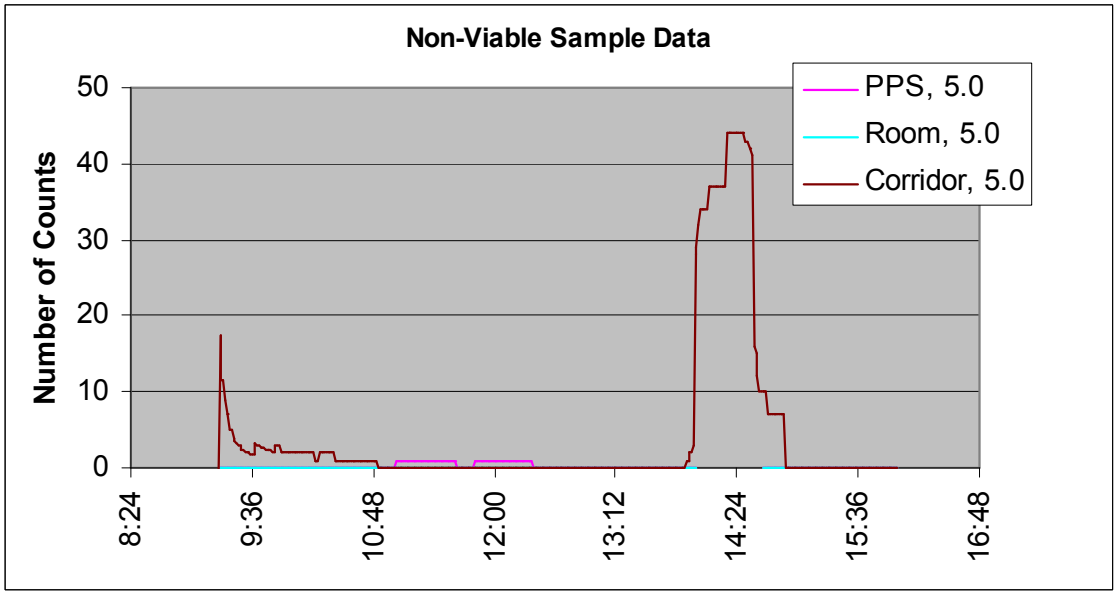


Figure 4.50 - Non-viable Particulate Trend, 5.0 micron, Phase 8

Phase 8 Conclusion

With the modifications completed, this third run of dynamic testing successfully completed processing of 651, 4mL oval, white SPP bottles. All environmental data was collected, trended, and remained within established operating limits throughout processing.

Additional improvements are noted as, per the research plan, the first of the three required sterility runs is next.

Phase 9 – Modifications and Sterility Test #1

Always in the process of adjustment and continuous improvement, in-line flow controls were added to the singluator motions in preparation for the 1st research sterility run. Also designed and fabricated were longer support posts to the right side guide rail to enable greater adjustment and a dedicated ultrasonic horn wrench as the horn and bottle grippers are now removed and moist heat sterilized prior to each production use.

Added to the rotary in feed table was a new way to transfer oval bottles to the conveyor. Designed was a round, plastic, center spacer that pivots on the center drive stub of the rotary table. This removable disc is sized to accommodate two thicknesses of the oval bottles so that bottles are indexed from trays into the gap formed between the rotary infeed table wall and the rotating edge of the center disc.

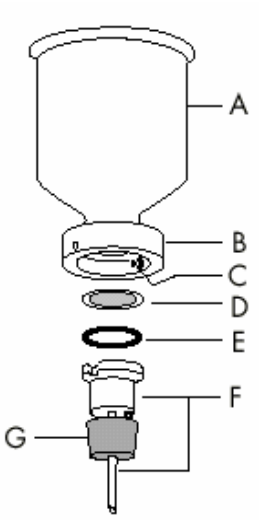
The final challenges for the PPS for full acceptance and release for routine production use was a series of three sterility challenges. The sterility challenges, for

acceptance, must pass all sterility, personnel and environmental testing in three consecutive production simulation runs. Each challenge is a full simulation of normal processing including any anticipated user interventions.

Phase 9, the first sterility or media (as this is the medium pooled and tested) challenge, went off with some difficulty as this first run presented a difficult challenge in terms of the product to be processed, the personnel involved and the time allotted.

The Product Pooling System was sanitized in the aseptic room in preparation for processing. Also prepared was the receiving carboy. This 10L capacity glass carboy was moist heat (steam) sterilized at 121 deg C for 60 minutes with a top rubber stopper or closure prepared with a hydrophobic 0.2 micron rated vent filter.

Also steam sterilized for the test run was the stainless steel collection funnel as illustrated in Figure 4.51, misc. tools which may be needed and the titanium ultrasonic horn and stainless steel bottle grippers as these components are the most at risk of product contact during transfer.



A - Funnel & Locking Ring Assembly
B - Locking Ring
C - Nylon lockwheels
D - Filter Support Screen
E - Support Screen gasket
F - Funnel Base
G - Carboy Stopper

These are the specifications for the Stainless 47 mm Filter Holder:

Filter Size: 47 mm diameter	Filter Area: ~ 9.6 cm or 100 grid squares
Prefilter Size: 35 mm diameter	Funnel Capacity: 650 mL
Pressures: vacuum	Dimensions(mm): 114 dia.×229 height

Carboy Vent - 0.2µm PTFE (or equal) vent filter with tubing.

Note: Tube to direct solution into carboy must be approx. 5" long or have ~3" projection beyond carboy vent tube.

Figure 4.51 - Product Pooling System, Collection Funnel Information & Setup

The system was prepared with correct change parts for the bottle to be processed. The bottle processed was a clear, SPP material bottle, containing a transparent liquid media. This presented opportunities as the reflective photo sensors had difficulty distinguishing between bottles present at a given station vs. not present.

In addition the bottles were overfilled which meant at times liquid was actually up in the neck area of the bottle. This presented problems as the target ultrasonic cutting area became very limited. Oval bottles as mentioned earlier are very unstable, especially on moving systems. Their foot print is narrow and wide and, when liquid filled, have a high center of gravity. The net result was 1018 bottles processed out of a target maximum of 1800. Frequent interventions or adjustments to the PPS occurred. Interventions were primarily due to the need to upright fallen oval bottles.

Furthermore, this was the first time two of assigned scientists were involved with operating the PPS so training was also included in this processing.

Processing time was further limited to 2 hours in the morning session and 2 ½ hours in the afternoon session. Actual processing time was less due to sanitization and sampling and setup. Remaining cycle time resulted in 3.8 bottles per minute or 15.8 seconds per bottle. This is compared to a measured cycle time of 14.4 seconds per bottle using a 4 second drain time previously. Drain time for this run was reduced to 0.30 seconds after slowing down the 180 degree rotation of the bottle to drain.

An issue with the filled oval bottles was, at the start of the run, when the bottle was quickly inverted to drain the open outlet was essentially blanked off by the

contained liquid seeking to exit as a result of the vacuum in the bottle keeping the liquid from draining. An air break was needed to initiate flow through the opened bottle. For this reason a change was made to restrict the flow of the pneumatic actuator serving to rotate the bottle 180 degrees. This restriction slowed the inversion time from 1 second to nearly 5 seconds. This slow movement allowed air to be inhaled into the bottle thus breaking the vacuum and allowing the liquid to drain. The PPS is designed for versatility. Flow controls are built into every movement and motion to accommodate these special processing needs. Demonstrating this adjustment further added to the "hands on" training provided to scientists.

Summary data for the run is outlined in Table 4.19.

Table 4.19 - Test Phase 9, 1st Sterility Processing Summary

Bottle Tested	=	4ml SPP Oval (clear)	
Horn Height	=	52	mm
Drain Time	=	0.30	seconds
Quantity Processed	=	1000	
PE Settings			
PE 1	=	1045	
PE 2	=	280	
PE 3	=	239	
PE 4	=	538	
Processing Time	=	265	minutes
Measured Cycle Time	=	15.9	seconds
Pooled Solution Weight	=	3614.9	grams
Target Fill Volume per Bottle	=	3.8	grams
% Solution Recovery	=	95.1	

Environmental data for this phase of testing is reflected by Figures 4.52 through 4.56. Noted is that all parameters are within limits and are considers as “passing” for the run.

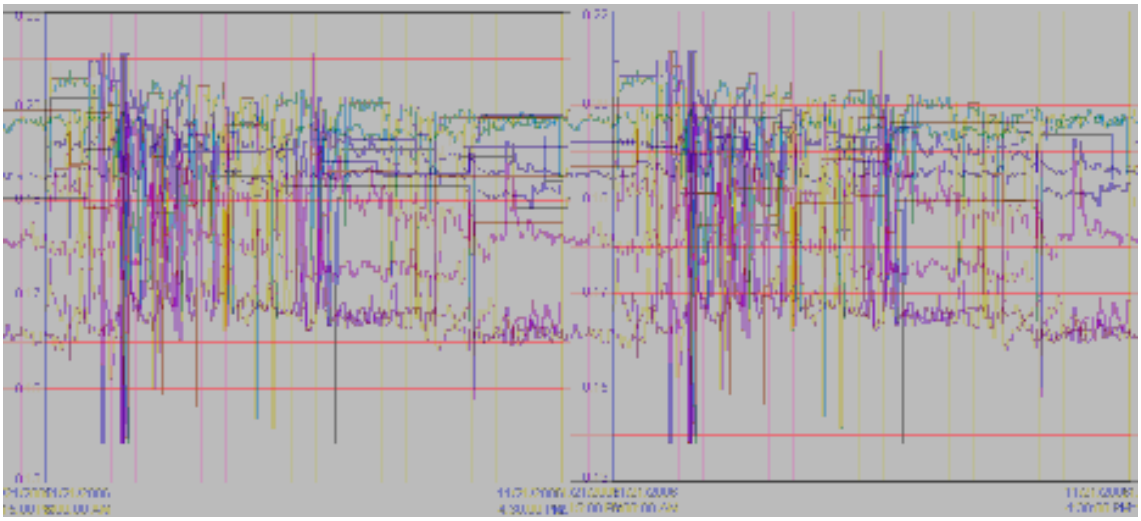


Figure 4.52 - Differential Pressure Trend, Phase 9

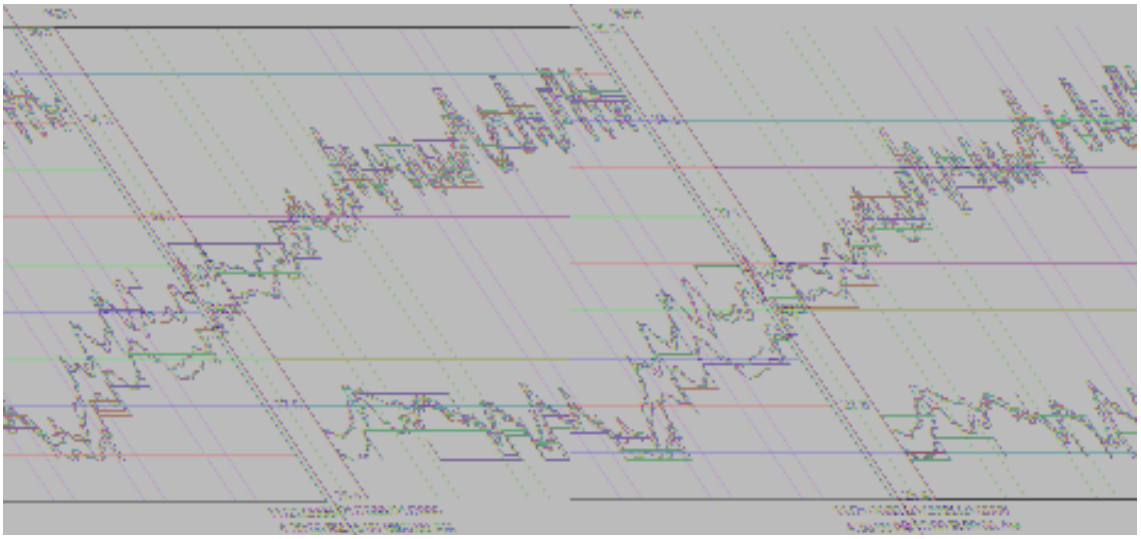


Figure 4.53 - Relative Humidity Trend, Phase 9

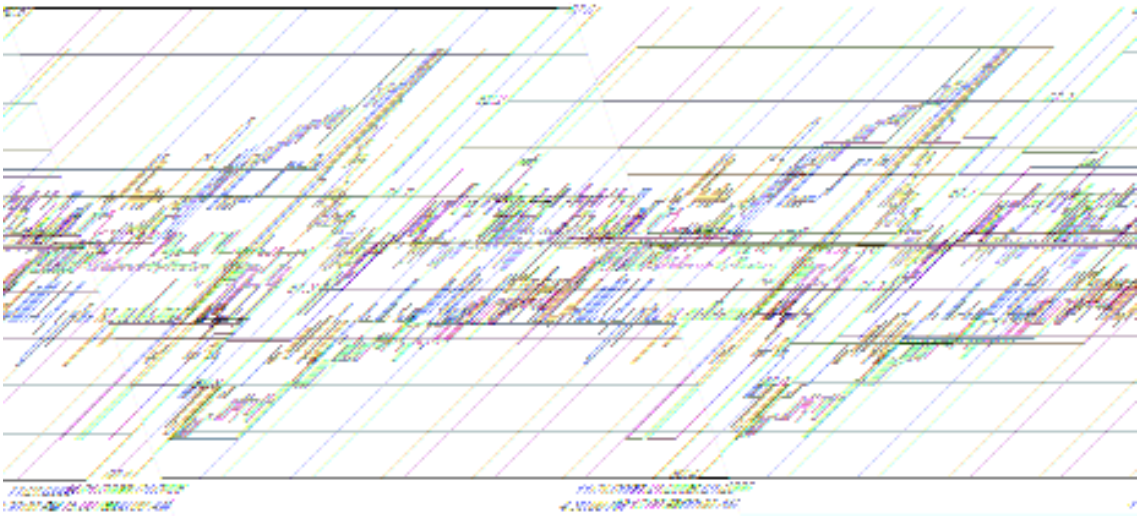


Figure 4.54 - Temperature Trend, Phase 9

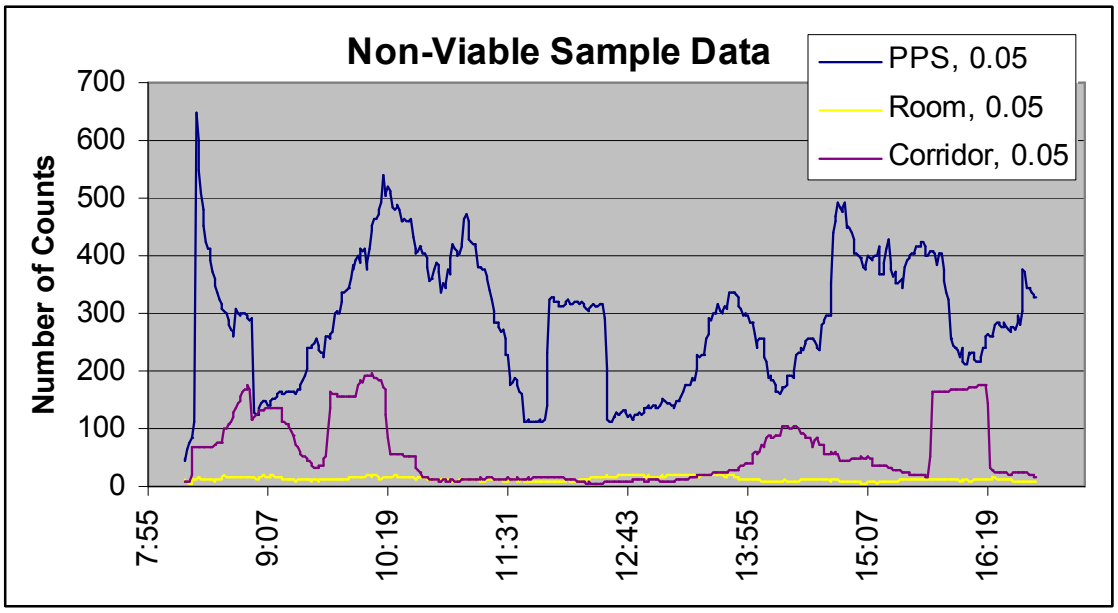


Figure 4.55 - Non-viable Data Trend, 0.05 micron, Phase 9

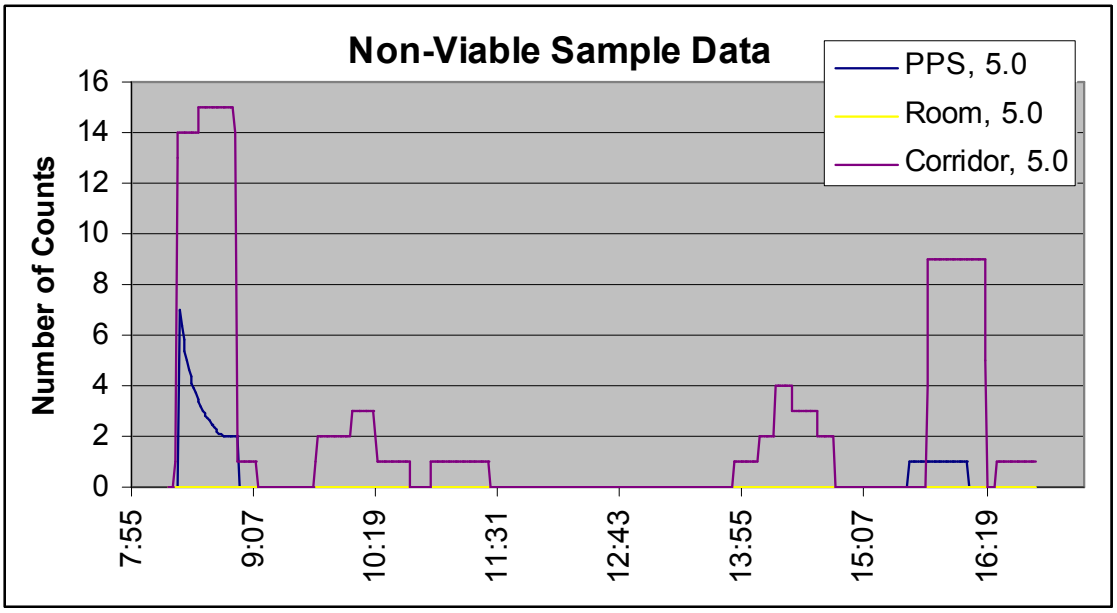


Figure 4.56 - Non-viable Data Trend, 5.0 micron, Phase 9

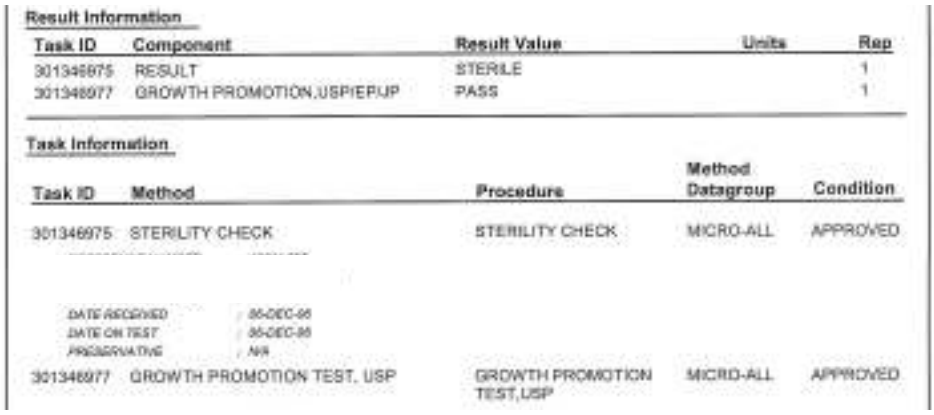
Note: Raw data is included in the Appendix.

Phase 9 Conclusion

Solution used for the 1st media pooling simulation was soybean casein digest medium (3% W/V %) with sterile water. Data and adverse events aside, the critical challenge for this first run remains the sterility of the pooled solution. 3614.9g of solution was collected and placed in incubation for 14 days, 7 at 30-35 deg C and 7 at 20-25 deg C.

Analytical results reported after incubation followed by an additional 7 days of accelerated growth promotion seem somewhat anti climatic but is the most welcome of

news. As shown in Figure 4.57 all testing results are reflected as sterile, passing and approved.



Result Information

Task ID	Component	Result Value	Units	Rep
301346975	RESULT	STERILE		1
301346977	GROWTH PROMOTION,USP/EP/JP	PASS		1

Task Information

Task ID	Method	Procedure	Method Datagroup	Condition
301346975	STERILITY CHECK	STERILITY CHECK	MICRO-ALL	APPROVED
	DATE RECEIVED : 05-DEC-05 DATE ON TEST : 05-DEC-05 PRESERVATIVE : N/A			
301346977	GROWTH PROMOTION TEST, USP	GROWTH PROMOTION TEST,USP	MICRO-ALL	APPROVED

Figure 4.57 - Sterility Results, Phase 9

One run successfully completed, two to go.

Phase 10 – Sterility Test #2

With the gained knowledge from the phase 9 test run, further identified changes were implemented. Changes included a new access door such that users do not have to open the entire door panel to clear bottle jams, ref. Figure 4.58. This smaller door minimizes the disruption of air flow.

Figure 4.58 – Added Access Door

In parallel to this change the bypass switch was also removed from the control panel which by passed the safety interlock for this door. The switch, originally intended for those products which require special mixing and placement one by one on the conveyor, remains behind the operator control panel but for routine operations this door now behaves like all others where the PPS comes to a stop when any door is opened.

Also fabricated was a new non-viable isokinetic sampling probe support to keep it clear of initial setup and adjustments of the PPS motions, reference Figure 4.59.

Figure 4.59 – Added Sample Probe Support Bracket

The most significant change implemented for this Phase 10 test was the engineering change to aim the reflective sensors off the bottle cap instead of the body of the bottle. Sensor brackets were redesigned to increase there aiming height and proximity to the source and further greatly increase there adjustability in every direction via the new quick-clamp multi-axis supports. Figure 4.60 show the revised sensor support design made up of two 316 stainless steel plates with slotted holes, overlapping each other with a thumb screw clamping them into the desired position.

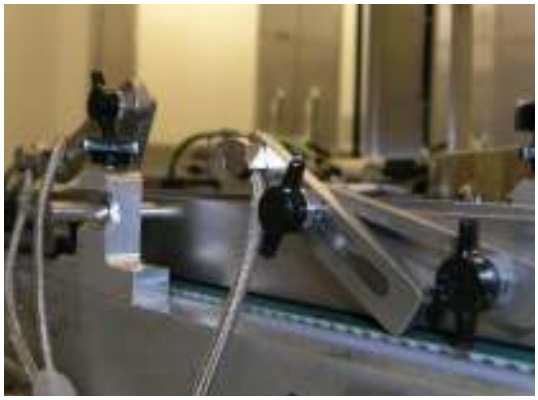


Figure 4.60 – Reengineered Sensor Support Bracket

Phase 10, the second media challenge, went off without difficulty. This second run processed 15mL media filled LDPE round bottles.

The Product Pooling System was sanitized in the aseptic room in the same manner in preparation for processing. Also prepared and sterilized were two 20L receiving glass carboys with the titanium ultrasonic horn, stainless steel bottle grippers and accessories as before.

The system was prepared with correct change parts for the round bottle to be processed. The bottle processed was a clear, LDPE material, round bottle, containing a transparent liquid media. Corrections made since the first run performed extremely well especially in sensing the bottle cap as bottles moved through the system.

Travel of the round bottles is very stable during movement vs. oval due logically to the surface footprint of the round and its lower center of gravity. Oval bottles behave like “bowling pens” as they wobble freely through the PPS rotary or linear movements.

The net result was 1,550 bottles processed out of a target maximum of 1800. Frequent interventions or adjustments to the PPS occurred. Interventions were primarily up righting fallen oval bottles.

Table 4.20 - Test Phase 10, 2nd Sterility Processing Summary

Bottle Tested	=	15ml LDPE Round (clear)	
Horn Height	=	68	mm
Drain Time	=	0.80	seconds
Quantity Processed	=	1550	
PE Settings			
PE 1	=	1045	
PE 2	=	2000	
PE 3	=	2500	
PE 4	=	2500	
Processing Time	=	310	minutes
Measured Cycle Time	=	12	seconds/bottle
Pooled Solution Weight			
Carboy #1 (750 bottles x 15mL each)	=	10,512.2	grams
Carboy #2 (800 bottles x 10mL each)	=	7831.3	grams
% Solution Recovery	=	95.3	

Particulate Testing

Initiated in this phase of testing was an investigational study, never conducted previously on the manual process, to quantify the number and relative size of any particulates within the pooled solution.

Recall that sterility of the solution is determined via the microbial growth (viable) characteristics of the media processed, accelerated by incubation. Non-viable particulates also are very undesirable and have specific limits defined by the USP.

The United States Pharmacopeia–National Formulary (USP–NF) is a book of public pharmacopeial standards. It contains standards for medicines, dosage forms, drug substances, excipients, medical devices, and dietary supplements.

The U.S. Federal Food, Drug, and Cosmetics Act designates the USP–NF as the official compendia for drugs marketed in the United States. A drug product in the U.S. market must conform to the standards in USP–NF to avoid possible charges of adulteration and misbranding. The USP–NF is also widely used by manufacturers wishing to market therapeutic products worldwide. Meeting USP–NF standards is accepted globally as assurance of high quality.

The United States Pharmacopeia (USP) is the official public standards-setting authority for all prescription and over-the-counter medicines, dietary supplements, and other healthcare products manufactured and sold in the United States. USP sets standards for the quality of these products and works with healthcare providers to help them reach the standards. USP's standards are also recognized and used in many other countries outside the United States. These standards have been helping to ensure good pharmaceutical care for people throughout the world for more than 185 years.

USP is an independent, science-based public health organization. As a self-sustaining nonprofit organization, USP is funded through revenues from the sale of products and services that help to ensure good pharmaceutical care. USP's contributions to public health are enriched by the participation and oversight of volunteers representing pharmacy, medicine, and other healthcare professions as well as academia, government, the pharmaceutical industry, health plans, and consumer organizations.

Non-viable particulates contained within the pooled solution are evaluated per strict guidelines for ophthalmic solution defined within Unites States Pharmacopeia

(USP) 28, Physical Tests/<788> Particulate Matter in Injections, Pages 2448 – 2454 and <789> Particulate Matter in Ophthalmic Solutions, Pages 2454 – 2455 using either a specified and proven particle analyzer or by microscopic inspection. Procedures are used for determining particulate matter contamination of aqueous solutions by analysis using a HIAC analyzer (instrument specific to particle analysis), based on the current USP general test <788> Particulate Matter in Injections.

Particulate matter consists of mobile, randomly-sourced, extraneous substances, other than gas bubbles, that cannot be quantitated by chemical analysis due to the small amount of material that it represents and to its heterogeneous composition. Injectable solutions, including solutions constituted from sterile solids intended for parenteral use, is essentially free from particulate matter that can be observed on visual inspection. The tests described herein are physical tests performed for the purpose of enumerating subvisible extraneous particles within specific size ranges.

Microscopic and light obscuration procedures for the determination of particulate matter are given herein. This chapter provides a test approach in two stages. The injection is first tested by the light obscuration procedure (stage 1). If it fails to meet the prescribed limits, it must pass the microscopic procedure (stage 2) with its own set of test limits. Where for technical reasons the injection cannot be tested by light obscuration, microscopic testing may be used exclusively. Documentation demonstrating that the light obscuration procedure is incapable of testing the injection or produces invalid results is required in each case. It is expected that most articles will

meet the requirements on the basis of the light obscuration test alone; however, it may be necessary to test some articles by the light obscuration test followed by the microscopic test to reach a conclusion on conformance to requirements.

All large-volume injections for single-dose infusion and those small-volume injections for which the monographs specify such requirements are subject to the particulate matter limits set forth for the test being applied, unless otherwise specified in the individual monograph. Excluded from the requirements of this chapter are injections intended solely for intramuscular and subcutaneous administration.

Not all injection formulations can be examined for particles by one or both of these tests. Any product that is not a pure solution having a clarity and a viscosity approximating those of water may provide erroneous data when analyzed by the light obscuration counting method. Such materials may be analyzed by the microscopic method. Emulsions, colloids, and liposomal preparations are examples. Similarly, products that produce air or gas bubbles when drawn into the sensor, such as bicarbonate-buffered formulations, may also require microscopic testing. Refer to the specific monographs when a question of test applicability occurs. Higher limits are appropriate for certain articles and will be specified in the individual monographs.

In some instances, the viscosity of a material to be tested may be sufficiently high so as to preclude its analysis by either test method. In this event, a quantitative dilution with an appropriate diluent may be made to decrease viscosity, as necessary, to allow the analysis to be performed.

In the tests described below for large-volume and small-volume injections, the results obtained in examining a discrete unit or group of units for particulate matter cannot be extrapolated with certainty to other units that remain untested. Thus, statistically sound sampling plans based upon known operational factors must be developed if valid inferences are to be drawn from observed data to characterize the level of particulate matter in a large group of units. Sampling plans should be based on consideration of product volume, numbers of particles historically found to be present in comparison to limits, particle size distribution of particles present, and variability of particle counts between units.

This procedure is suitable for determining the presence and number of particles over an extended range including larger than or equal to 10 μm, 25 μm and 50 μm. The HIAC is designed specifically for particulate analysis in small and large-volume parenterals. The HIAC particle sensor utilizes the principle of light extinction (obscuration) to detect particles. The liquid sample flows through the sample cell where the laser diode beam has been projected. When no particles are present, the total beam reaches the detection photodiode. When particles are present within the sample cell, the particle blocks the laser beam thereby producing an electrical pulse for each particle. The pulse amplitude, or decrease in the intensity of the beam, is proportional to the particle size. The photodiode pulses are amplified to the signal strength expected by the counter and are transferred to the counter. The counter identifies the quantity and

height of the pulses by sorting the pulses into bins with predefined pulse amplitude ranges.

A particle counter meeting the requirements of the current USP <788> monograph is required. Two instruments from HIAC have been shown as suitable. They are the model 8000A particle counter with a model 3000 liquid sampler in conjunction with a HRLD 150 liquid sensor, and a model 9064 particle counter with a model 3000A liquid sampler in conjunction with a HRLD 150 liquid sensor. Both are available from HIAC/ROYCO Instruments, Division of Pacific Scientific, 141 Jefferson Drive, Menlo Park, CA 94025.

USP <788> general test states that the instrument used is to be calibrated and should have acceptable sensor resolution and have an accurate sampling apparatus. It also states that the sensor should be calibrated with 10, 15 and 25 micron monosized polystyrene spheres before use.

The number of particles per mL is calculated by the Model 8000A analyzer or by the PDAS application as follows:

$$P_v = \frac{\bar{c}}{V_p}$$

Where: P_v = Number of particles/mL

$\bar{c}$ = Average particle count of all portions analyzed.

V_p = Volume of each portion analyzed (mL).

This microscopic method provides conditions for performing Particulate Matter Test for Ophthalmic Solutions also based on USP <788> and USP <789>. This method is only applicable for the testing of Particulate Matter in Ophthalmic Solutions only.

Microscope - The microscopic particulate matter test may be applied to both large-volume and small-volume injections. This test enumerates subvisible, essentially solid, particulate matter in these products on a per volume or per container basis, after collection on a microporous membrane filter. Some articles cannot be tested meaningfully by light obscuration. In such cases, individual monographs specify only this microscopic assay. Solutions exempted from analysis using the microscopic assay are identified on a monograph basis. Examples are solutions that do not filter readily because of high viscosity (e.g., concentrated dextrose, starch solutions, or dextrans). In performance of the microscopic assay do not attempt to size or enumerate amorphous, semiliquid, or otherwise morphologically indistinct materials that have the appearance of a stain or discoloration on the membrane surface. These materials show little or no surface relief and present a gelatinous or film-like appearance. Since in solution this material consists of units on the order of 1 μm or less, which may be counted only after aggregation or deformation on an analytical membrane, interpretation of enumeration may be aided by testing a sample of the solution by the light obscuration particle count method. Compound trinocular microscope equipped with photographic capabilities. It should be equipped with a mobile stage, circular diameter graticule, NIST certified micrometer system graduated in 10μm increments, an internal episcopic top light

illuminator. The eyepiece and objective combination must give a magnification of 100X (e.g. Nikon Eclipse ME600 Microscope).

Evaluation of Results - Filter Membrane Blank Results - In this procedure, 90mLs is the recommended volume of purified water for the filter membrane blank. The "Filter Blank" specification stated in USP <788> is based upon a 50mL volume. The specification for the 90mLs volume was based upon the count per ml equivalent to the USP using the 50mL.

The specifications for 50mLs and 90mLs are as follows:

50mLs: NMT 20 particles ≥10µm, NMT 5 particles ≥25µm

90mLs:NMT 36 particles ≥10µm, NMT 18 particles ≥25µm

Note: The specifications for the Filter Membrane Blank should be calculated for any volume based up the counts/ml equivalent to the specifications listed in USP<788>.

Sample Results calculation:

The calculations that are required to obtain the sample results are as follows:

Volume in mL $V = \frac{W1 - W2}{D}$

Particles/mL $= \frac{P}{V}$

Where: W1 = Initial weight

W2 = Final weight

D = Density of the formulation

P = Number of particles counted

V = Sample volume in mLs

Result interpretation, per USP <789>, the sample specifications are as follows:

NMT 50 particles/mL ≥10µm

NMT 5 particles/mL ≥25µm

NMT 2 particles/mL ≥50µm

Results from this first ever and extensive particulate testing for Phase 10 are illustrated in Figure 4.61.

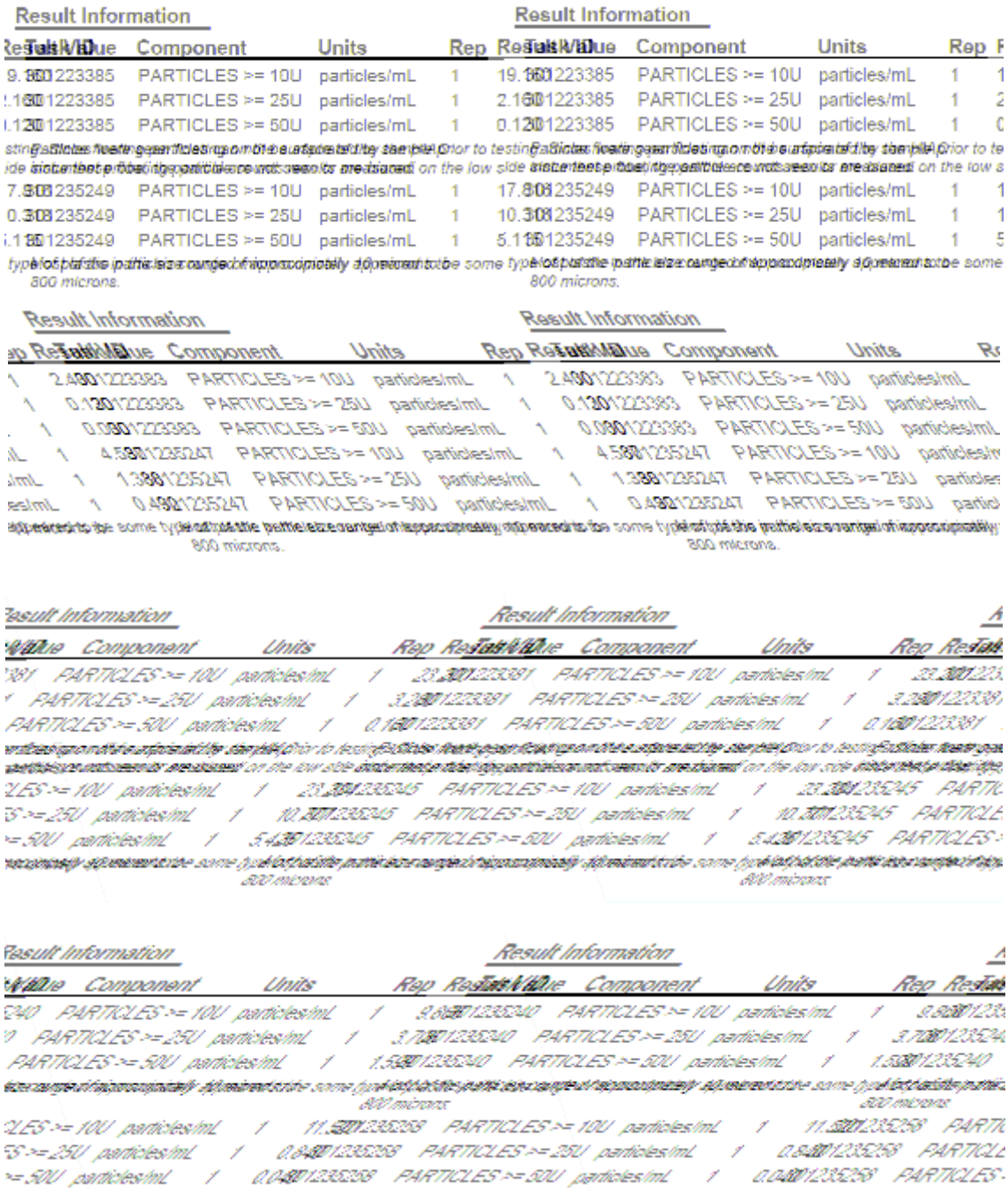


Figure 4.61 - Phase 10 Particulate Results, Carboy #1

Because this phase of research included pooling solution into two separate collection containers, for comparison, Carboy #1 utilized the product collection funnel without a screen and Carboy #2 used the same funnel with a screen as depicted in Figure 4.51.

Just as in the old manual process, plastic particles are noted floating on the surfaces of the pooled solution. These particles, never before quantified, are not noted for Carboy #2 but are visually observed and further analyzed for Carboy #1.

The carboy #1 particles (ref. Figure 4.61) are found to be within acceptable limits in the 10, 25 and 50 micron range. Larger particles, noted up to 800 micron in size, lead to the full implementation of the Figure 4.51 product collection funnel with included screen.

Phase 10 Environmental Data

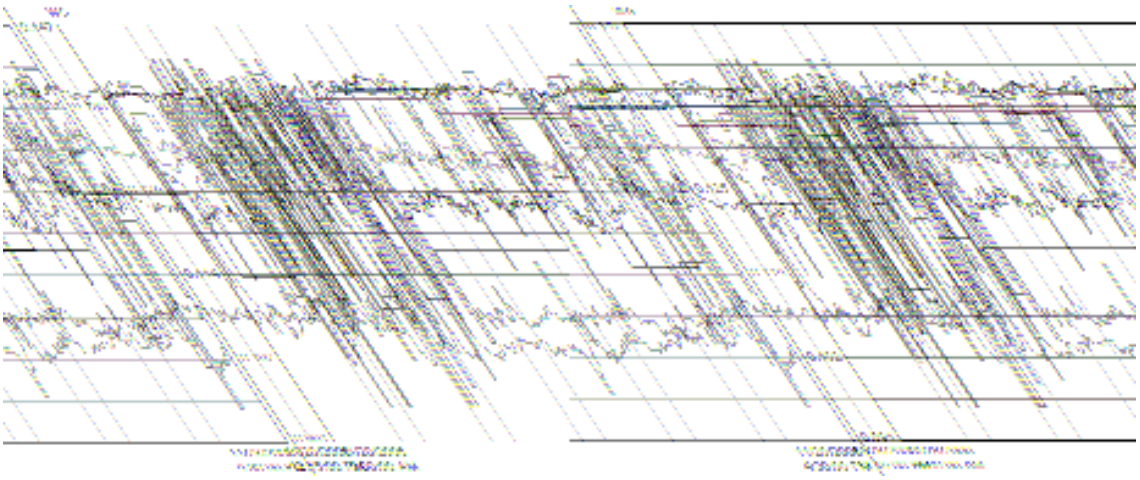


Figure 4.62 - Differential Pressure Trend, Phase 10

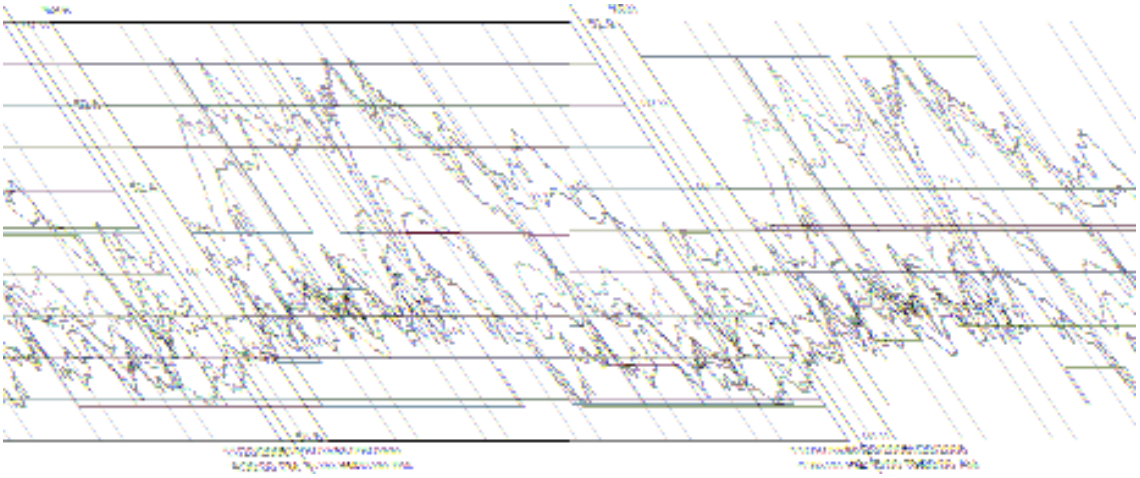


Figure 4.63 - Relative Humidity Trend, Phase 10

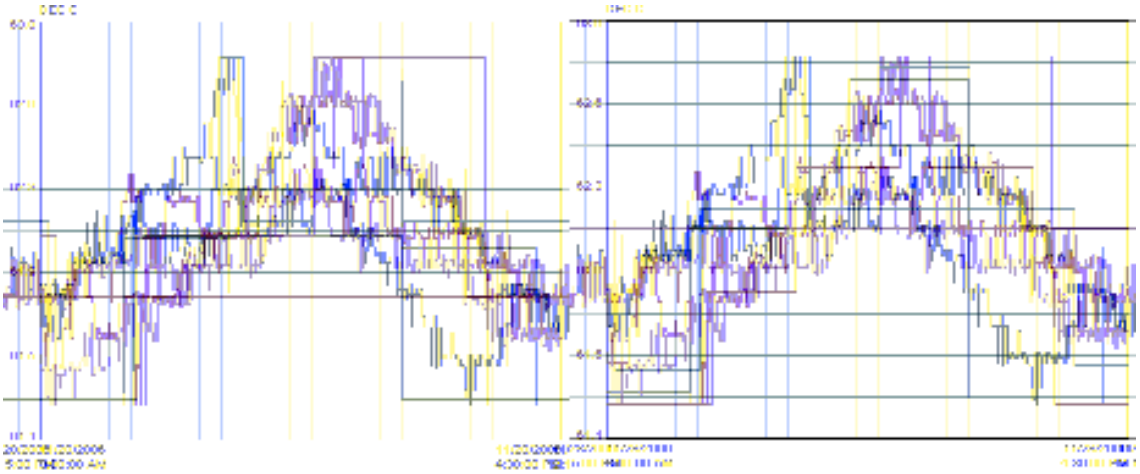


Figure 4.64 - Temperature Trend, Phase 10

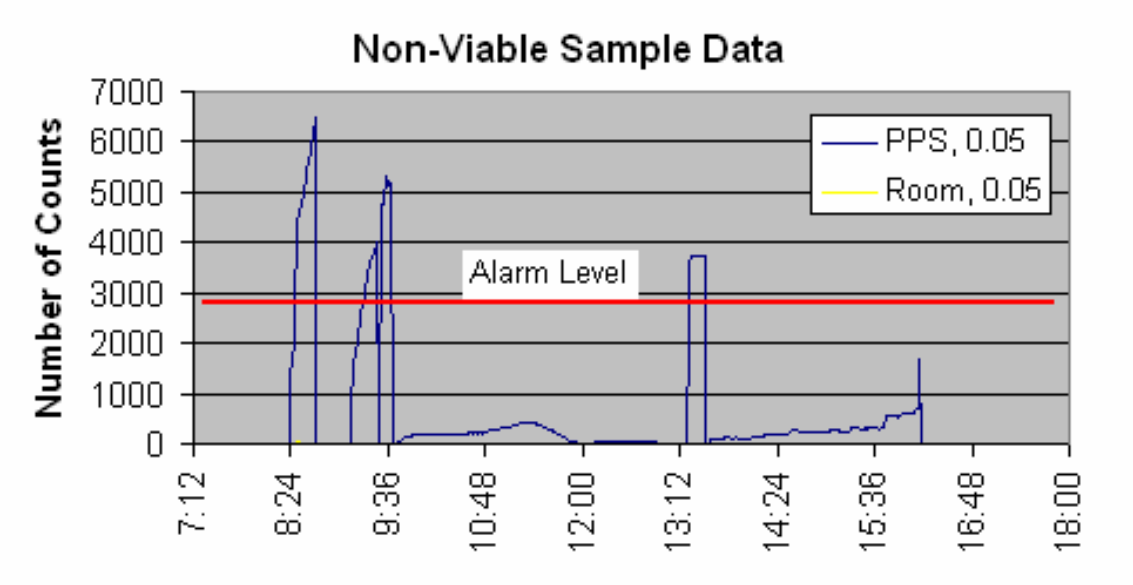


Figure 4.65 - Non-viable Data Trend, 0.05 micron, Phase 10

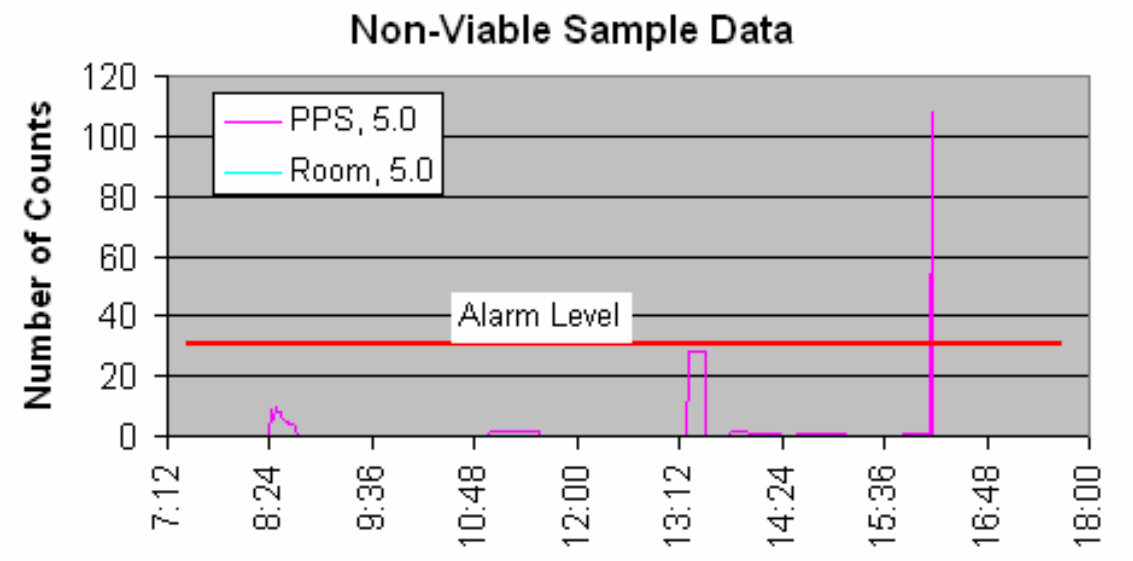


Figure 4.66 - Non-viable Data Trend, 0.05 micron, Phase 10

Phase 10 Conclusion

Analytical results reported for the second media challenge after incubation and an additional 7 days of accelerated growth promotion are again welcome news. As shown in Figure 4.67 all testing results for each of the two pooled solutions are reflected as sterile, passing and approved.

Result Information

Task ID	Component	Result Value	Units	Rep
301350883	STERILITY OF BULK SAMPLE	STERILE		1
301350885	GROWTH PROMOTION,USP/EP/JP	PASS		1

Task Information

Task ID	Method	Procedure	Method Datagroup	Condition
301350883	MEDIA FILL,STERILITY,BULK	STERILITY, MEDIA FILL	MICRO-ALL	APPROVED
	PROCEDURE NUMBER : 0001119 *DATE RECEIVED : 13-DEC-06* *DATE ON TEST : 13-DEC-06* *PRESERVATIVE : N/A*			
301350885	GROWTH PROMOTION TEST, USP	GROWTH PROMOTION TEST,USP	MICRO-ALL	APPROVED

Result Information

Task ID	Component	Result Value	Units	Rep
301350887	STERILITY OF BULK SAMPLE	STERILE		1
301350889	GROWTH PROMOTION,USP/EP/JP	PASS		1

Task Information

Task ID	Method	Procedure	Method Datagroup	Condition
301350887	MEDIA FILL,STERILITY,BULK	STERILITY, MEDIA FILL	MICRO-ALL	APPROVED
	DATE ON TEST : 13-DEC-06 *PRESERVATIVE : N/A*			
301350889	GROWTH PROMOTION TEST, USP	GROWTH PROMOTION TEST,USP	MICRO-ALL	APPROVED

Figure 4.67 - Sterility Results, Phase 10
Two research runs now successfully completed and documented, one to go.

Phase 11 – Sterility Test #3

The third, and final, sterility research run was completed using yet another bottle configuration not yet processed to date and an additional processing challenge never before researched.

Bottle configuration and the overall summary of the test is listed in Table 4.21.

Table 4.21 - Test Phase 11, 3rd Sterility Processing Summary

Bottle Tested	=	15ml LDPE Round (clear)	
Horn Height	=	68	mm
Drain Time	=	0.60	seconds
Quantity Processed	=	2000	
PE Settings			
PE 1	=	845	
PE 2	=	1600	
PE 3	=	2100	
PE 4	=	1500	
Day 1 Processing Time	=	310	minutes
Measured Cycle Time	=	12	seconds/bottle
Day 2 Processing Time	=	310	minutes
Measured Cycle Time	=	12	seconds/bottle
Pooled Solution Weight			
Carboy – Day 1 (1200 bottles x 15mL each)	=	10,512.2	grams
Carboy – Day 2 (800 bottles x 10mL each)	=	7831.3	grams
% Solution Recovery	=	95.3	

The PPS is an entirely new, never seen before, automated system. Users don't know what to do. Throughout the research process all known process challenges have been successfully met. Therefore, pressure builds form the scientists to throw in new challenges which are beneficial to those scientists performing the process.

An observation of machine design and processing in general, if you are successful, as confidence in a system grows, the desire to challenge the system to the point of failure also grows.

The additional challenge involved in this phase of research is a two day processing challenge. The desire was to challenge the PPS, environment and personnel to process and pool sterile solution one day, hold the solution overnight, and then continue processing, adding to the pooled solution, the second day.

Environmental Data

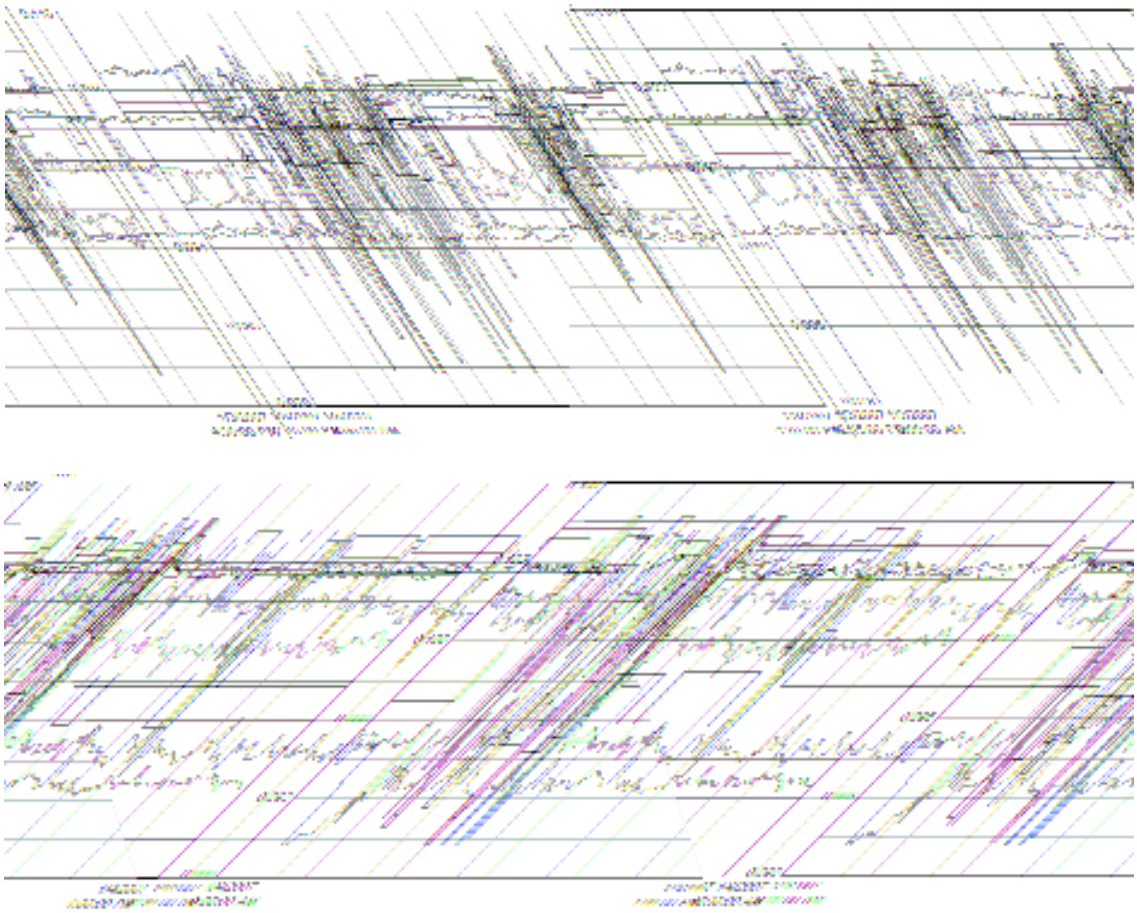


Figure 4.68 - Differential Pressure Trend, Phase 11

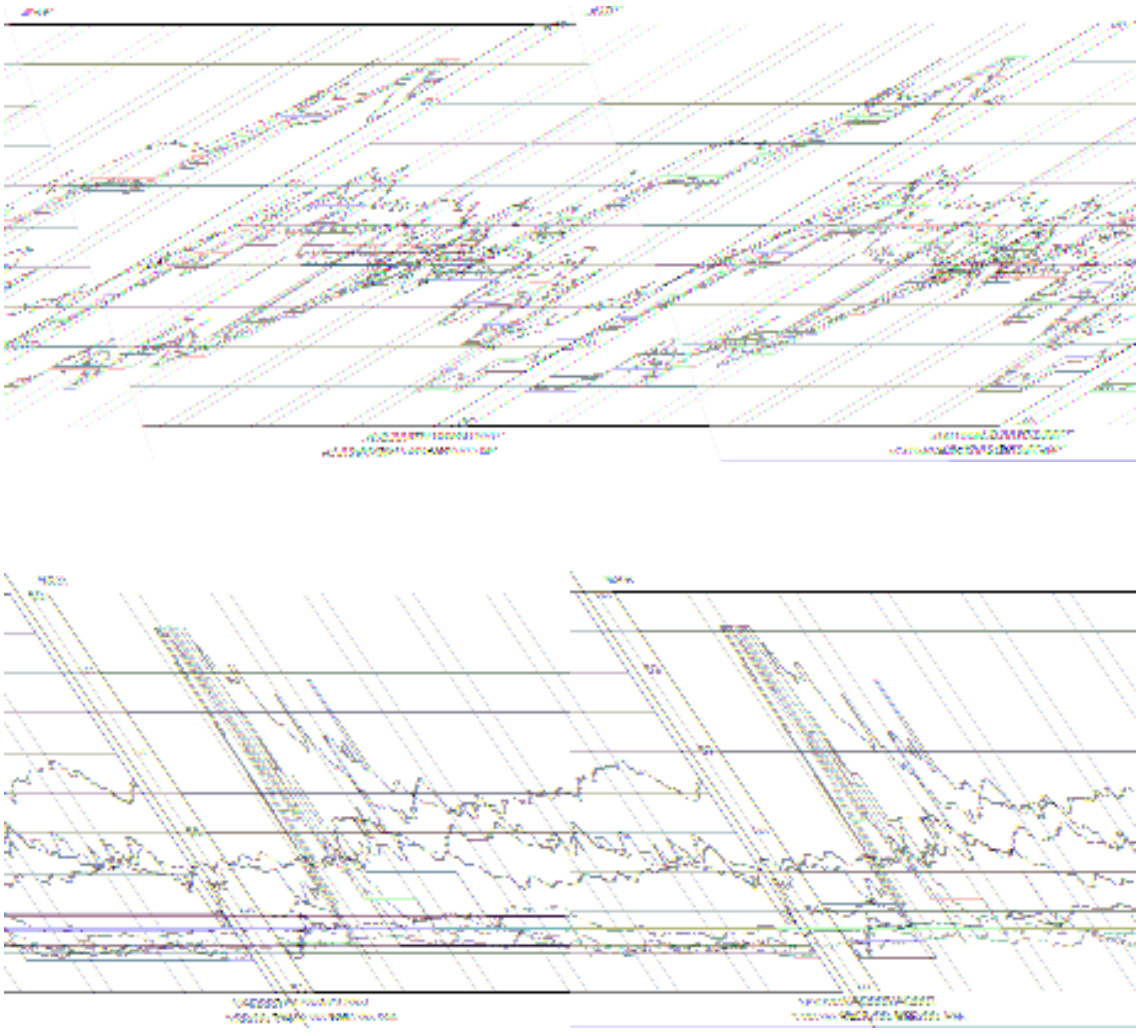


Figure 4.69 - Relative Humidity Trend, Phase 11

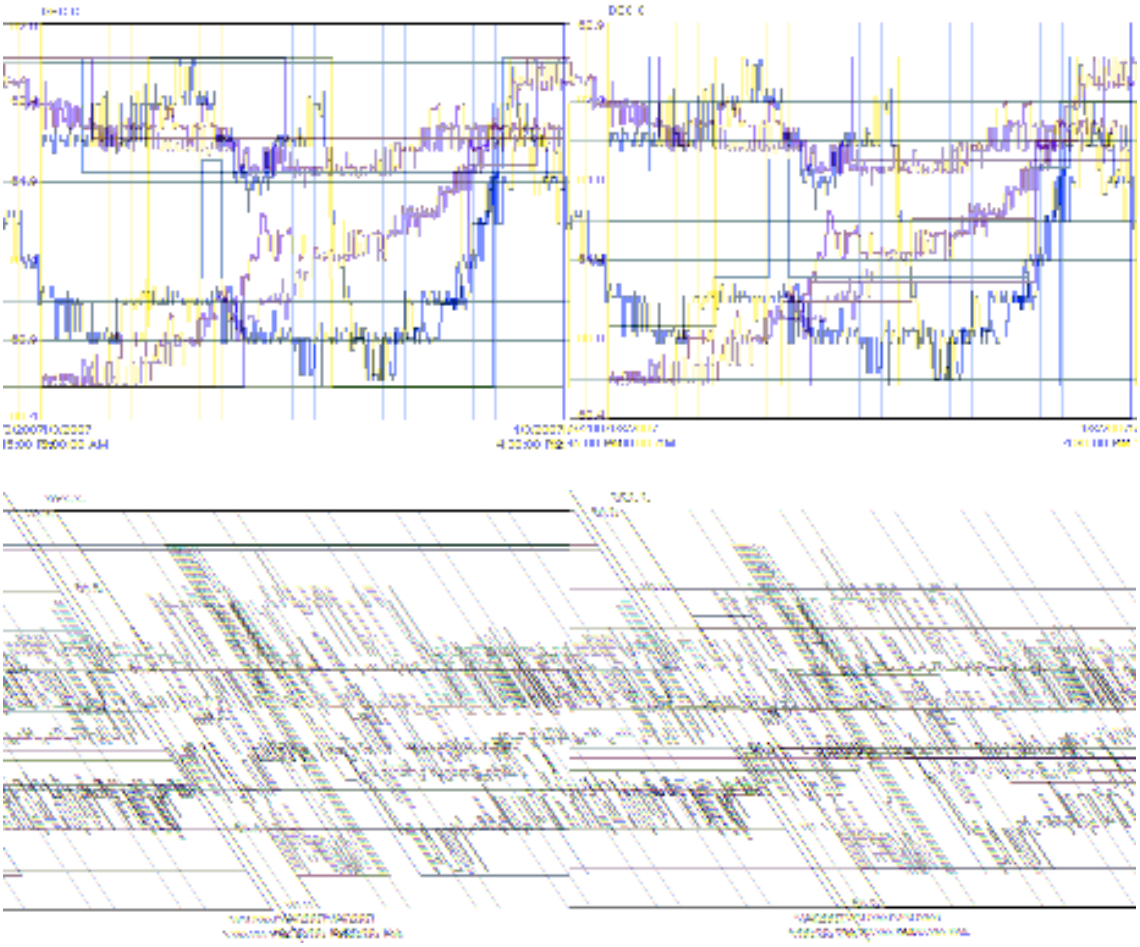


Figure 4.70 - Temperature Trend, Phase 11

The above environmental data trends once again proofed all stayed within set limits. Note on Figure 4.69 and 4.70 that upon personnel entering the area, as seen previously, that an initial spike is observed. This is a short time as people and PPS operation initially creates a heat load which required a short time for the HAVC system to respond and overcome, all the while keeping temperature within limits. Temperature control for the processing area has quick responding temperature control with sensors

installed in the return air duct so that measured air flow can be sensed and supply air can be adjusted as needed before the return air even makes it back to the air handler. Sterile processing areas have >200 air changes per hour that comprise about 90% re-circulating air and 10% fresh air make-up to assure the relative positive pressure in the processing room.

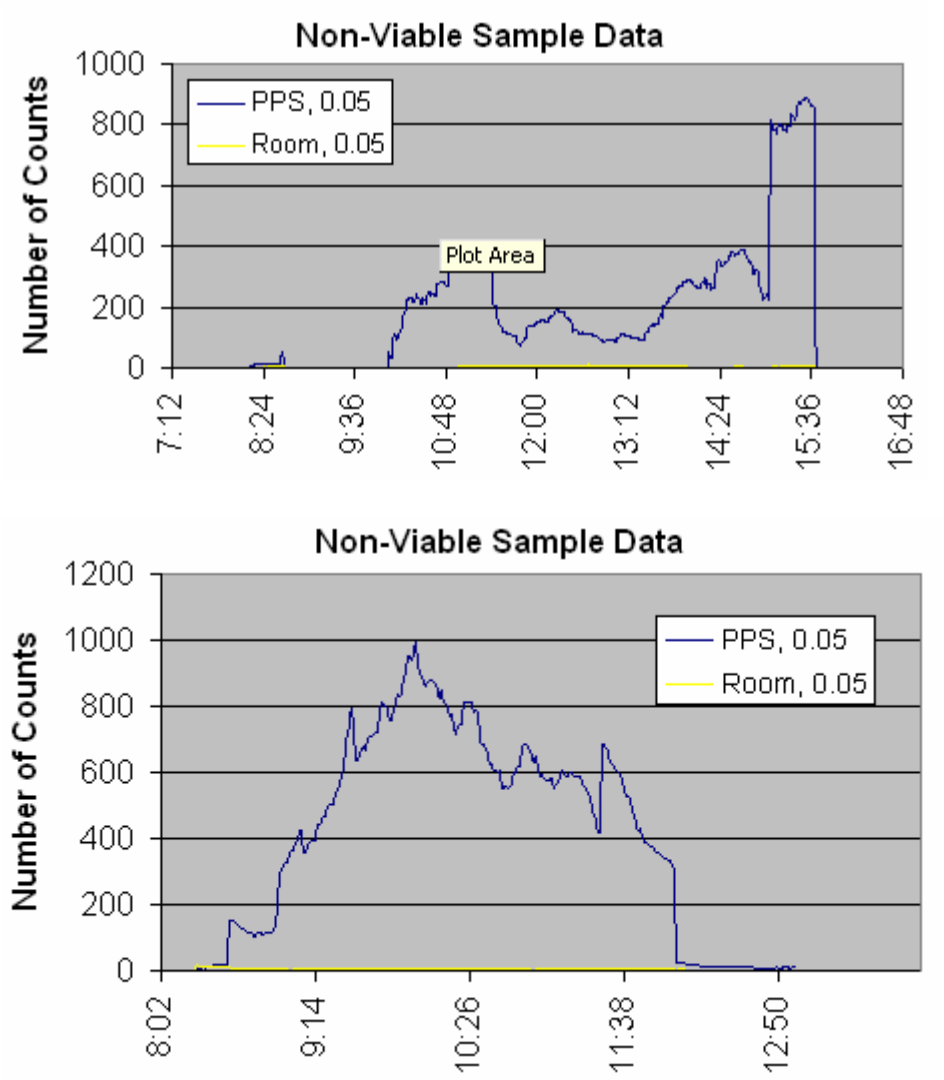
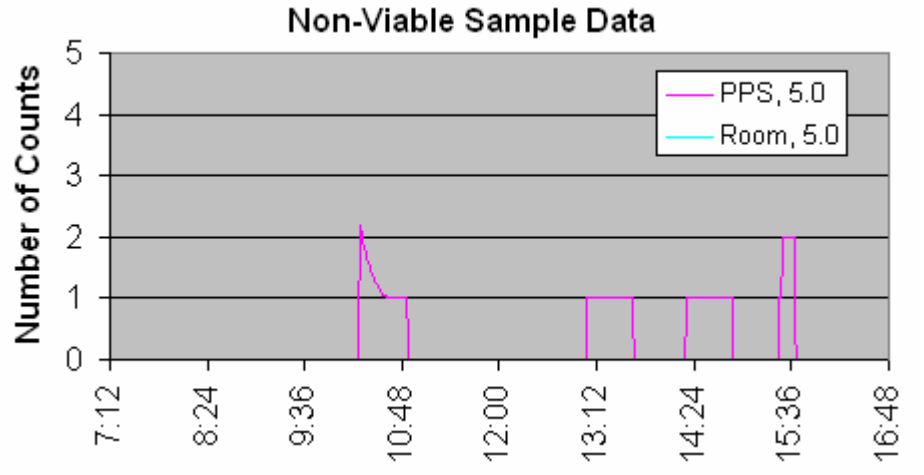


Figure 4.71 - Non-viable Data Trend, 0.05 micron, Phase 11



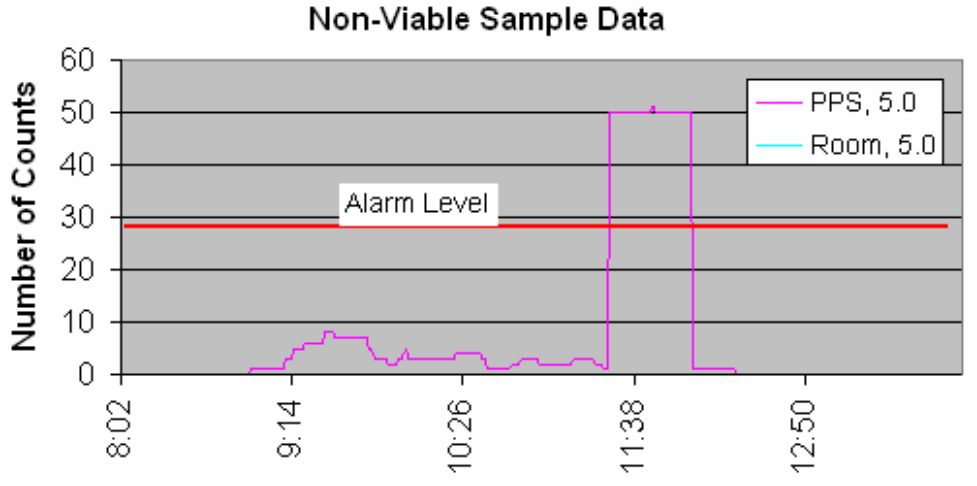
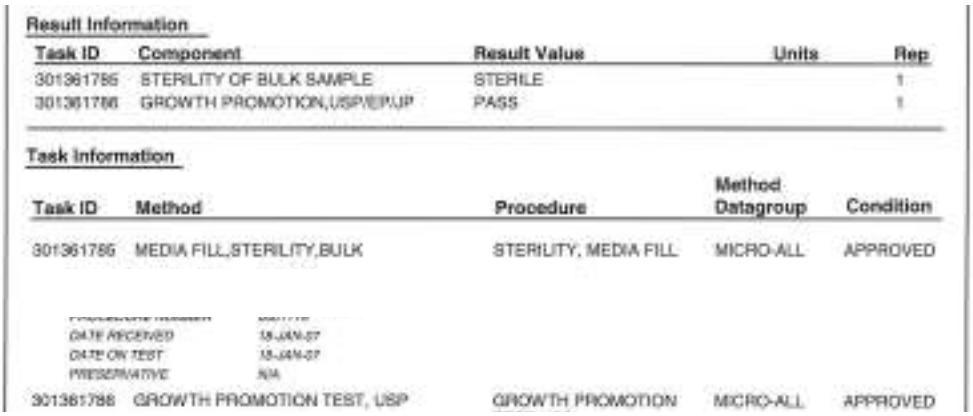


Figure 4.72 - Non-viable Data Trend, 5.0 micron, Phase 11

Figure 4.72 shows alarm level non-viable particulate counts on day 2 of processing. This occurred after processing was complete and clean up had begun. Typically, particle count analyzers are turned off after processing but in this case were inadvertently left on.



Result Information

Task ID	Component	Result Value	Units	Rep
301361785	STERILITY OF BULK SAMPLE	STERILE		1
301361786	GROWTH PROMOTION,USP/EP/JP	PASS		1

Task Information

Task ID	Method	Procedure	Method Datagroup	Condition
301361785	MEDIA FILL,STERILITY,BULK	STERILITY, MEDIA FILL	MICRO-ALL	APPROVED
	DATE RECEIVED 18-JAN-07			
	DATE ON TEST 18-JAN-07			
	PRESERVATIVE N/A			
301361786	GROWTH PROMOTION TEST, USP	GROWTH PROMOTION	MICRO-ALL	APPROVED

Figure 4.73 - Sterility Results, Phase 11

CHAPTER 5

SUMMARY OF RESULTS

Research demonstrated and documented that the Product Pooling System (PPS) consistently performs as intended throughout all anticipated operating ranges under all actual operational conditions. Results ensured that pre-established acceptance criteria were met to ensure acceptable use of and production from the system, releasing the system for routine production use per established procedures.

This dissertation summarizes the successful completion of the research related to the development, definition, deployment and implementation of the Product Pooling System.

The Product Pooling System (PPS) is an all-inclusive, portable system comprised of five fully automated operating stations, reference Figure 5.1. Bottles travel one by one through the system for processing.

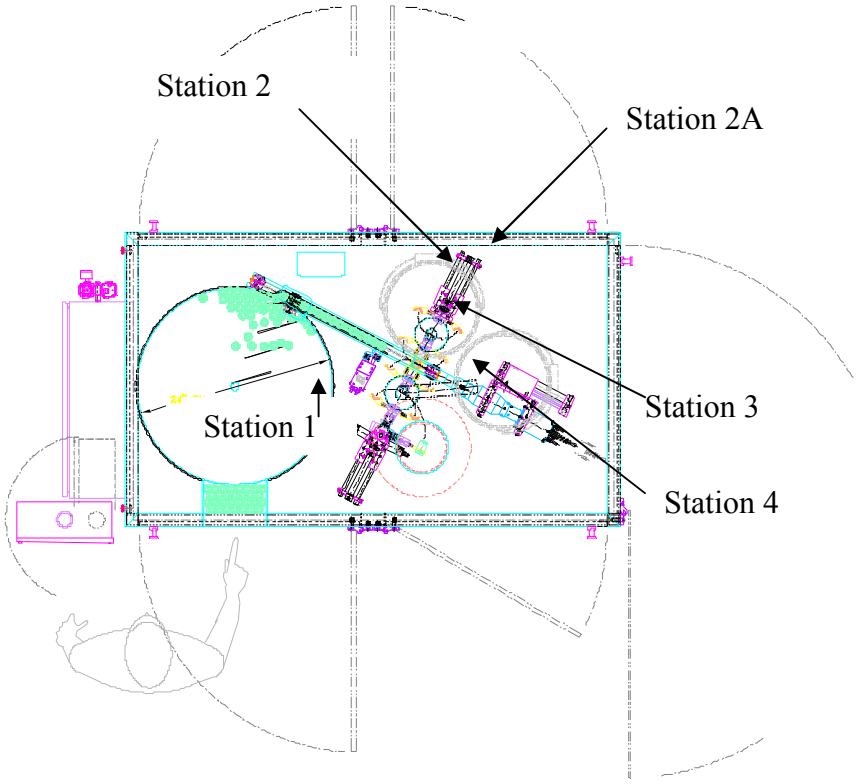


Figure 5.1 - Product Pooling System, Plan View

Following is a brief summary of the PPS operating sequence, stated business use and intended purpose, instruments used during weighing of pooled solution, additional required documentation (separate from this document), additional air flow verification and lastly, a summary of the final phase of performance research including summary of data collected and analyzed for each run.

5.1 Sequence of Operations

Station 1 - Bottles are manually unloaded from a tray or otherwise placed by an operator onto a rotary infeed table which in turn feeds a conveyor serving as staging for Station 2.

Station 2 – Consists of a singulator which releases bottles one by one towards the ultrasonic separator which comprises a wash-down style transducer (with air cooling), booster, and a knife edge horn, mounted to an air powered slide.

Station 2A – This station includes two automatic grippers which, when a bottle is present, advances to grip the bottle. The first gripper advances to grip the bottle body or lower section (i.e. the portion containing sterile solution), the second gripper advances to grip the upper portion of the bottle (i.e. bottle cap with dropper insert). When the bottle is determined to be gripped properly the ultrasonic horn is advanced to remove (cut off) the bottle upper portion. The bottle upper portion is next automatically discarded into a waste receptacle at Station 2A. Station 2 and 2A each are adjustable, having the ability to be manually raised and lowered using a hand lead screw to position them to accommodate different bottles sizes.

Station 3 - The bottle body or lower section is next automatically moved and further rotated or inverted to pour contents into the Station 4 product collection container. The remaining empty bottle is then automatically discarded into the Station 3 waste

collection container (note that the Station 2A and 3 waste collection containers are typically one in the same).

Station 4 – Pre-sterilized product collection container dedicated to each production run. This container is typically a glass carboy with a collection funnel at the inlet sterilized and prepared for each production run. Smaller carboys may be used in combination with risers as needed. The production collection container is closed and sealed at the end of each production run and stored for future use.

5.2 Intended Use/Business Purpose

Researchers should always have, in writing a intended use and business purpose statement for the focus of their work. This does not have to be wordy, elaborate statement, but rather should be a simple summary statement at the earliest phase of research. The statements may certainly be revised as research progresses. Following are the final statements relative to the PPS.

The "Intended Use" of this system is to provide for the automated transfer of sterile solution within a packaged (i.e. sealed) plastic container and gather it into a secondary container for future use, and further discard the top and bottom portion (i.e. bottle body, bottle neck, cap insert) from which the solution originated.

The "Business Purpose" of this system is to operate within a aseptic environment by trained personnel processing sterile filled and sealed plastic round or

oval bottles and aseptically collect/pool the contained liquid into a prepared sterile vessel for future use.

5.3 Instruments

The following table lists the calibrated test instruments utilized during execution of this research. All equipment/instruments requiring calibration were in current calibration prior to and during research testing.

Table 5.1 - Calibrated Equipment/Instrument Summary

Instrument Description	ID No.	Date of Calibration	Date Used	Next Cal. Due:
Product Pooling System	518624	N/A	9/15/06-1/4/07	N/A
Weigh Balance	A2978	10/13/06	11/21/06	04/2007
Weigh Balance	A2978	10/13/06	11/28/06	04/2007
Weigh Balance	A2978	10/13/06	1/3/07	04/2007
Weigh Balance	A2978	10/13/06	1/4/07	04/2007

5.4 Pretesting Documentation

Prior to execution of the performance of research, documentation, as summarized in Table 5.2, was authored and verified as available and complete.

Table 5.2 - Documentation Summary

Document Description
Installation and Operational Protocol
IOQ Technical Report
Standard Operating Procedures
Standard Batch Records
Training Verification

5.5 Airflow Verification

The objective of this test function was to verify that adequate unidirectional airflow within and around the PPS enclosure (Plexiglass Shields) existed as appropriate for the room classification and to document testing performed.

Testing was successfully completed, using a sterile fog generator (dry ice and WFI) while video recording air flow patterns to observe and document air flow patterns to ensure adequate airflow exists. Results are summarized in Table 5.3.

By visual observation, the fog was observed being carried smoothly towards the floor, in a general downward direction, with no evidence of swirling, up flow or eddies in critical areas. Fog also passed on the outside of safety shields and was not drawn into the enclosure, including when personnel walked by shield. For historical reference, video taping was completed and reviewed, labeled and stored.

Table 5.3 - Air Flow Pattern Summary

Test Area	Static		Dynamic	
	Pass	Fail	Pass	Fail
Airflow around the inner perimeter of the PPS upper enclosure.	✓		✓	
Airflow around the outer perimeter of the PPS upper enclosure.	✓		✓	
Airflow across the tray load inlet to rotary table, outside shield.	✓		✓	
Airflow inside enclosure around the bottle gripping/ultrasonic horn station.	✓		✓	
Airflow inside enclosure through product collection opening.	✓		✓	
Airflow inside room (at approximately 30" below face of HEPA filters) near doors, walls, windows is unidirectional downwards and exits area.	✓		✓	
Airflow across the top of operator panel.	✓		✓	

5.6. Aseptic Media Simulation/Pooling

Objective of this test function was to demonstrate the ability of the Product Pooling System in total, including personnel, support systems, supporting processes, components and environment, to aseptically pool sterile solution under production conditions, ultimately proofing beyond any reasonable doubt that the sterility of the pooled solution is maintained after processing

Additionally, routine environmental data was monitored, the Product Pooling System sanitization procedure was challenged and viable surface sampling was completed.

This test function was performed a total of three (3) runs with the third run split, held overnight, and completed a second day.

Each run was successfully completed with passing results.

Testing (reference Table 5.4) consisted of three consecutive, successful, media simulations, the third run occurred over two days (designated as run #3 and run #4), comprised of trained personnel processing sterile media filled units using the PPS within the controlled, aseptic, processing environment.

Table 5.4 - Sterility Summary

Run #	Run Date	Sterility Result	Growth Promotion Result
1	11/21/06	Sterile	Pass
2	11/28/06	Sterile	Pass
3	01/03/07	Sterile	Pass
4	01/04/07		

The sequence of events for each research simulation run are summarized as follows:

1. Room was sanitized prior to each run.
2. PPS components were prepared and sterilized.
3. Bottles to be processed are staged in trays, 100 per tray, placed on a cart in the transfer airlock and surface sanitized.

4. Day of processing – Personnel enter the area, garb and proceed to the processing room.
5. PPS is sanitized.
6. Non-viable sensors are confirmed to be on and operating normally.
7. Product collection carboy is setup.
8. Viable airborne sampling is setup and started.
9. Bottles are processed one by one as solution is pooled.
10. At the end of processing the pooled solution is sealed and removed.
11. Viable airborne sampling is stopped.
12. PPS viable surface sampling is completed.
13. PPS is sanitized.
14. Waste is gathered for disposal.
15. For this research, pooled product (media) is held, incubated and analyzed. Hold for each run was at room temperature for a minimum of seven (7) days, then transferred to a room temperature of 30-35°C for a minimum, additional, seven (7) days. This is then followed by a growth promotion test.

The PPS viable surface sampling (RODAC) results for each run are summarized in Table 5.5. All results were within limits and passing.

Table 5.5 - Surface Viable Sampling Summary

Seq.	RODAC Location	Results (CFU/cm$^{2)}$ per Run #				Limit	In Spec? (Y/N)
		#1	#2	#3	#4		
1	Access Door (exterior)	0.0	0.0	0.0	0.0	0 - 0.1	Y
2	Access Door (interior)	0.0	0.0	0.0	0.0	0 - 0.1	Y
3	Access Door (exterior)	0.0	0.0	0.0	0.0	0 - 0.1	Y
4	Access Door (interior)	0.0	0.0	0.0	0.0	0 - 0.1	Y
5	Access Door (exterior)	0.0	0.0	0.0	0.0	0 - 0.1	Y
6	Access Door (interior)	0.0	0.0	0.0	0.0	0 - 0.1	Y
7	Access Door (exterior)	0.0	0.0	0.0	0.0	0 - 0.1	Y
8	Access Door (interior)	0.0	0.0	0.0	0.0	0 - 0.1	Y
9	Access Door (exterior)	0.0	0.0	0.0	0.0	0 - 0.1	Y
10	Access Door (interior)	0.0	0.0	0.0	0.0	0 - 0.1	Y
11	Rotary Infeed Table	0.0	0.0	0.0	0.0	0 - 0.1	Y
12	Top of Ultrasonic Knife	0.0	0.0	0.0	0.0	0 - 0.1	Y
13	Rotary Infeed Table	0.0	N/A	0.0	0.0	0 - 0.1	Y
14	Top of Platform	0.0	0.0	0.0	0.0	0 - 0.1	Y
15	Top of Collection carboy	0.0	0.0	0.0	0.0	0 - 0.1	Y
16	Operator Control Panel Face	0.0	0.0	0.0	0.0	0 - 0.1	Y
17	Portable Tray Cart	0.0	0.0	0.0	0.0	0 - 0.1	Y
18	Portable Vial Tray	0.0	0.0	0.0	0.0	0 - 0.1	Y
19	Portable Vial Tray	0.0	0.0	0.0	0.0	0 - 0.1	Y
20	SUM Highest CL	0.0	0.0	0.0	0.0	0 - 0.1	Y
21	Room Entry Door (exterior)	0.0	0.0	0.0	0.0	0 - 0.1	Y
22	Room Entry Door (interior)	0.0	0.0	0.0	0.0	0 - 0.1	Y
23	Phone Panel	0.0	0.0	0.0	0.0	0 - 0.1	Y
24	Wall	0.0	0.0	0.0	0.0	0 - 0.1	Y
25	SUM Highest CL	0.0	0.0	0.0	0.0	0 - 0.1	Y
26	Floor Surface	0.0	0.0	0.0	0.0	0 -1.0	Y

Airborne sampling occurred continuously during each research run. Results are as summarized in Table 5.6. All results were within limits and passing.

Table 5.6 - Airborne Viable Sampling Summary

Run #	Component	Elapsed Run time (minutes)	Results-Colonies/plate			Limit (CFU/m^3)	In Spec? (Y/N)
			Bacterial	Fungal	Total		
1	STA Count	437	0	0	0	0.-0.1	Y
2	STA Count	390	0	0	0	0.-0.1	Y
3	STA Count	335	0	0	0	0.-0.1	Y
4	STA Count	147	0	0	0	0.-0.1	Y

Routine personnel monitoring was also completed after each run with results as listed in Table 5.7. All results were within limits and passing.

Table 5.7 - Personnel Gown/Glove Sample Summary

Run #1			**RESULTS**				
			Scientist Number				
Sample Site	**Plate ID**	**Limit**	**A**	**B**	**C**	**D**	**In Spec? (Y/N)**
Neck Area/Upper Chest	3 (Rodac)	0-0.5 CFU/cm^2	0	0	0	0	Y
Forearm	4 (Rodac)	0-0.5 CFU/cm^2	0	0	0	0	Y
Glove Palm	5 (Rodac)	0-0.1 CFU/cm^2	0	0	0	0	Y
Gloves (All 10 Fingers)	3 (Touch Plate)	0-1.0 CFU/plate	0	0	0	0	Y

Table 5.7 - continued

Run #2			**RESULTS**				
Neck Area/Upper Chest	3 (Rodac)	0-0.5 CFU/cm^2	0	0	0	0	Y
Forearm	4 (Rodac)	0-0.5 CFU/cm^2	0	0	0	0	Y
Glove Palm	5 (Rodac)	0-0.1 CFU/cm^2	0	0	0	0	Y
Gloves (All 10 Fingers)	3 (Touch Plate)	0-1.0 CFU/plate	0	0	0	0	Y
Run #3			**RESULTS**				
Neck Area/Upper Chest	3 (Rodac)	0-0.5 CFU/cm^2	0	0	0	0	Y
Forearm	4 (Rodac)	0-0.5 CFU/cm^2	0	0	0	0	Y
Glove Palm	5 (Rodac)	0-0.1 CFU/cm^2	0	0	0	0	Y
Gloves (All 10 Fingers)	3 (Touch Plate)	0-1.0 CFU/plate	0	0	0	0	Y
Run #4			**RESULTS**				
Neck Area/Upper Chest	3 (Rodac)	0-0.5 CFU/cm^2	0	0	0	N/A	Y
Forearm	4 (Rodac)	0-0.5 CFU/cm^2	0	0	0	N/A	Y
Glove Palm	5 (Rodac)	0-0.1 CFU/cm^2	0	0	0	N/A	Y
Gloves (All 10 Fingers)	3 (Touch Plate)	0-1.0 CFU/plate	0	0	0	N/A	Y

Routine non-viable air particulate sampling occurred continuously during each run reporting at two particle sizes, 0.5 and 5.0 micron. Table 5.8 summarizes the particle count data for both particles sizes for each of the two sampling probes, one

within the PPS enclosure (above the product collection area) and the second probe within the room.

Table 5.8 - Non-Viable Environmental Data Summary

Values represent number of particles counted per cubic meter of air sampled.

Sample Location -->	PPS, 0.5	PPS, 5.0	Room, 0.5	Room, 5.0
Run #1				
Min	44	0	5	0
Max	648	7	21	0
Average	291	0	13	0
minutes in alarm	0	0	0	0
minutes in alarm during processing	0	0	0	0
Run #2				
Min	0	0	0	0
Max	6493	108	25	0
Average	661	2	13	0
minutes in alarm	41(1)	1(1)	0	0
minutes in alarm during processing	0	0	0	0
Run #3-Day ½				
Min	0	0	0	0
Max	887	2	10	0
Average	207	0	3	0
minutes in alarm	0	0	0	0
minutes in alarm during processing	0	0	0	0
Run #4 - Day 2/2				
Min	0	0	0	0
Max	993	51	18	0
Average	415	8	5	0
minutes in alarm	0	35(1)	0	0
minutes in alarm during processing	0	0	0	0

Note (1) - Alarm time occurred during run #2 for 42 minutes and run #4 for 35 minutes. Per procedure, processing was stopped during this time as adjustments were completed within the PPS enclosure while the sensor remained on.

Routine environmental data was trended and reviewed for each run in comparison to established limits, defined earlier in Table 4.52. Environmental data trend results were within limits for each research run.

Table 5.9 provides a summary for each research run with defining sanitization date, components processed, solution pooled, processing times and rates, and associated batch record.

Table 5.9 - Performance Research Phase Processing Summary

Run 1 Date: 11/21/06	Date Sanitized (prior to fill): 11/17/06
Run 2 Date: 11/28/06	Date Sanitized (prior to fill): 11/27/06
Run 3/4 Date: 01/03 and 1/04/07	Date Sanitized (prior to fill): 01/02 and 01/03/07

Research Run No.: Fill Size (label claim)	**Start Time**	**End Time**	**Collection Vessel Weight**	**Calculated Bottles Per Minute**
			Net (grams)	
1: 4.3 mL	0845	1625	3614.9	3.3
2: 15.3 mL 10.3 mL	0849	1556	10,512.2 7831.3	9.3
3/4: 5.3 mL	0956 0851	1530 1113	2593.1 4096.3	9.6 9.8

Table 5.9 - continued

Component Part Numbers (Description):						
Run 1	Bottle:	281277 (4ml, SPP, oval)	Plug:	281217	Cap:	272857
Run 2	Bottle:	277082 (15ml NDT, LDPE, round) & 277087 (15ml NDT, LDPE, round)	Plug:	279092 & 279067	Cap:	277542 & 278102
Run 3/4	Bottle:	277002 (8ml NDT, HDPE, round)	Plug:	279092	Cap:	277542

CHAPTER 6

CONCLUSION AND NEXT STEPS

All objectives of this research have been successfully met and documented. After nearly 3 years of research, development, fabrication, testing, modification and finally deployment, the Product Pooling System (PPS) has been fully and successfully implemented as a system and method for the transfer of sterile solution.

- Research demonstrated and documented that the Product Pooling System (PPS) consistently performs as intended throughout all expected, and some unexpected, operating ranges and conditions.
- Results ensured that pre-established acceptance criteria were met supporting acceptable use of and production from the PPS, releasing the system for routine production use per established procedures.
- This dissertation documents and summarizes successful completion of all research.
- A manual process that previously required four or more scientists risking both product and personal injury now requires no more than two exerting minimal effort. The two serve to load bottles onto the infeed table, observe the automated operation and collect the pooled solution.

- Time required is less, cost of operations is less, and product sterility is assured.

In conclusion, this research has effectively solved an unsolved problem through unique research and development, and application of technology, to mitigate both product and personnel risk, and reduce cost of operations, as associated with the aseptic process for the pooling of sterile product.

This research has successfully applied system development and process improvement methodology by defining an automated system and method for removing the tops from individual sealed bottles and pooling the small volumes of liquid contained in each bottle together in a collection container while maintaining the sterility of the product liquid.

Next, is to continue to gain knowledge of the PPS through continued operation. Objectives are to improve cycle time through optimizing motions within the system. Experience also needs to be gained in terms of reliability of the system components (i.e. ultrasonic generator, sensors, actuators, conveyors…) over time to establish preventive maintenance guidelines to assure continued long term performance.

APPENDIX A

PPS SUPPORTING DOCUMENTS

A.1. SWOT Analysis

SWOT – Specific to Product Pooling System

1. Strengths
    - 1.1. Reliability
    - 1.2. Ergonomics
    - 1.3. Operator Safety
    - 1.4. Sterility Assurance
    - 1.5. Maintainability
    - 1.6. Portability
    - 1.7. Ability to utilize existing operating environment
    - 1.8. Ability to utilize existing operating personnel
    - 1.9. Need for fewer Operators (reduced resources)
    - 1.10. Cost Savings
2. Weaknesses
    - 2.1. Cost
    - 2.2. Operator training/ownership
    - 2.3. Automated system – risk of single sensor failure, power loss
    - 2.4. Mechanical system – risk of failure
3. Opportunities
    - 3.1. Continuous improvement of cycle time, debugging
    - 3.2. Optimize and reduce cost of operation; fewer operators
    - 3.3. System expansion in terms of variety of bottles processed; change parts for oval and irregular shaped bottles

4. Threats

4.1. Technology - Ultrasonic cutting capability

4.1.1. Material - Need for processing of bottles developed with a plastic that cannot be cut using ultrasonic or that generate particles during cutting

4.1.2. Physical Size – Need to process bottles that physically will not fit into in-feed system and/or are too wide for ultrasonic cutting horn, grippers…

4.2. Changes in the Competitive Environment – No adverse impact foreseen as related to this product innovation.

4.3. Changes in the Sociocultural Environment- Social and cultural influences cause changes in attitudes, beliefs, norms, customs, and lifestyles.

No adverse impact foreseen as related to this product innovation.

4.4. Changes in the Political/Legal Environment

No adverse impact or regulatory relief foreseen as related to this product innovation.

Note that regulatory actions by government agencies often restrict the activities of companies in affected industries. The American Disabilities Act of 1990 placed restrictions on the way firms construct their places of business and design jobs. Companies with significant investment facilities that did not comply with the law viewed its implementation as a major threat. On the other hand, companies that market products designed to assist disabled shoppers and employees saw the act as a key opportunity (Marketing Strategy, 1998).

As can be seen, it is important to identify political/legal threats and opportunities in order to keep an edge on the market (Austainer, 1999).

4.5. Changes in the Internal Organizational Environment

No adverse impact foreseen as related to this product innovation.

Various elements within an organization's internal environment can also have an impact on marketing activities. Changes in the structuring of departments, lines of authority, top management, or internal political climate can all create internal weaknesses that must be considered during the SWOT analysis as well as in the development of the marketing plan.

5. SWOT References

5.1. "Developing Your Strategic SWOT Analysis." Austrainer. 1999. http://www.austrainer.com/archives/1397.htm. (5 Dec. 1999).

5.2. Ferrell, O., Hartline, M., Lucas, G., Luck, D. 1998. Marketing Strategy. Orlando, FL: Dryden Press.

A.2. Product Requirements Definition

The components specific to this product requirements definition are outlined within this section per the below table of contents.

1. Purpose

   Design a system/product, which is of the "have need – find solution (pull)" type, used to support clinical trails and market studies, and is entitled "Product Pooling System or PPS". System replaces and automates the current manual process.

   Within a sterile processing environment, the PPS is used to collect sterile liquid solution from products, from either internal or external (e.g. competitors), into a sterile collection container. This container is then used in the re-packaging of the product. The repackaged product is used to support ongoing trials, blind studies, and competitive product market comparisons. This process is currently a manual, labor intensive, costly process which risks both personnel and sterility of the product being pooled.

   Idea for product is to automate the process with the design of a single machine utilizing automation and a potentially disruptive technology with the overall objectives of eliminating personnel risk, assuring product sterility and decreasing operating cost.

2. Scope

   2.1. From a technical viewpoint

   Fabricate a safe, ergonomic, automated portable machine, suitable for use in an aseptic environment, for the purpose of removing the cap, dropper insert, and upper neck off a labeled plastic eyedropper type bottle, pour the fluid into a secondary collection container for future use, and discard the bottle, cap and insert from which the solution originated into a collection container.

   2.2. From a business viewpoint

Provide a system and method to successfully and cost effectively meet the need for the sterile transfer and collection of product to support current and future Clinical and market studies.

3. Stakeholder Identification

   3.1. Users/Operators – Most important for success of system, ownership and operation.

   3.2. Engineering (Responsible for system functionality and performance, fitness for use)

   3.3. Management (Responsible for production and delivery)

   3.4. Internal Customers (Marketing, Study Directors, Clinical Studies group)

   3.5. External Customers (Regulatory agencies, Study participants)

4. Market Assessment and Demographics

   System is treated as proprietary, intellectual property, of the organization and is not intended to be distributed or otherwise marketed to any external market.

   Product is targeted to be used internally by all those functionally trained and responsible, within the organization, and provide a proprietary system and method which offers both cost efficiency and a competitive advantage to the organization.

5. Use Cases

   5.1. Internal

   Clinical supplies production group within Research and Development.

   5.2. External

   None.

6. Feature Set

   6.1. General Requirements

      6.1.1. Machine will be non-particle generating.

      6.1.2. Machine will be suitable for use by trained, fully garbed, operators within a sterile, controlled, processing environment, e.g. clean room.

      6.1.3. User controls exist in the form of an operator interface to start and stop each machine operation and alternatively initiate a fully automatic sequence. Operator interface will further alert the user as to current operating status and any active system alarms.

6.1.4. Overall machine control architecture to be Allen-Bradley® PLC based.

6.1.5. Machine will be electrically powered using regulated and flow adjustable compressed air as needed at each transfer point.

6.1.6. Machine is planned to require one (1) operator for normal operation.

6.2. Safety

The machine will be equipped with light beam barriers, or equal, as needed for operator safety. Wires and pressurized air hoses will be covered with energy chains for protection. Any additional safety equipment required will be provided by the purchaser, or added to the quote price.

6.3. Physical Size

6.3.1. Maximum Width – 40”

6.3.2. Maximum Height – 80”

6.3.3. Maximum Length – 60”

6.3.4. Physical Weight - Not specified except that lateral push force can not exceed 50 lbf.

6.4. Handling/Movement

6.4.1. System to be equipped with four casters, non-skid, non-marking type, two fixed, two swivel, all four to be equipped with brake or locking feature.

6.4.2. Lateral push force, from any direction, not to exceed 50 lbf.

6.4.3. System to be movable without lifting.

6.5. Energy Requirements

6.5.1. Electrical power supply to be minimum NEMA 4 rated using 220 volt, single phase, 20 amp, electrical supply.

6.5.2. Ultrasonics -> 30 or 40 KHz, 1200 watt minimum.

6.5.3. Compressed air pressure available at 90 psi, clean and dry.

6.6. Fabrication Cost

Estimated “turn key” build cost for CY05 is $65,000.

6.7. Materials of Construction

6.7.1. All materials must be compatible with surface sanitization methods including isopropyl alcohol, 30% by volume, diluted with sterile water, and products which are a stabilized blend of paracetic acid, hydrogen peroxide, and acetic acid which provide fast, effective microbial control.

6.7.2. Materials of choice are primarily 304 and 316 stainless steels. Stainless steels are high-alloy steels that have superior corrosion resistance than other steels because they contain large amounts of chromium.

6.8. System Inputs

Completed, sealed, pharmaceutical bottles containing sterile liquid product.

6.9. System Ouptut

A single collection container containing sterile, liquid, product.

7. Constraints

7.1. Resources requested are available and assigned.

7.2. Funding requested is allocated.

7.3. By responsible area, the level of authority at least meets the level of responsibility.

7.4. Technology - Use of ultrasonic and automation, in addition to mechanical design is assumed to meet all expectations based on sound engineering judgment and prototype testing results.

8. Requirements

8.1. Functional Requirements

8.1.1. Variable product processing using format change parts in terms of bottle geometry and fill size, e.g. round bottles, oval bottles, 2 ml fill, 125 ml fill…

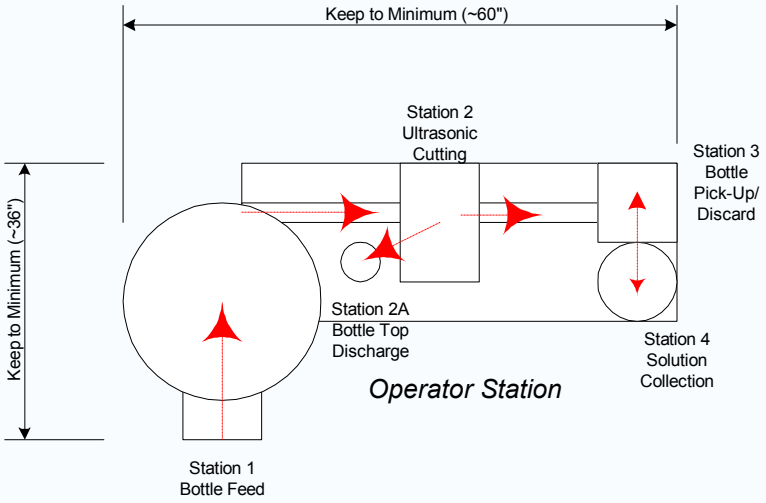
8.1.2. Cycle Time- Target average cycle time for a full cycle is eleven (11) seconds, allowing for five (5) bottles per min. with a maximum of (8) seconds per cycle or (7) bottles per min.

8.1.3. Cleanability for use within clean room – no corrosion, no particle generation.

8.1.4. Product Sterilty Assurance – no microbial gowth, i.e. positives, allowable on initial or periofidc media challenges.

8.2. Functional Description

8.2.1. Conceptual Plan



8.2.2. Proposed Sequence of Operations

8.2.2.1. Station 1 - Bottles will be placed by an operator onto a rotary feed table which in turn feeds a conveyor serving as staging for Station 2

8.2.2.2. Station 2 - Ultrasonics with a wash-down style transducer with air cooling, stainless steel booster, and a knife edge horn, mounted to an air slide.

8.2.2.2.1. Varying height and diameter of labeled round or oval bottles, or group of bottles, will be picked up or otherwise stopped or presented to the ultrasonic cutting station

8.2.2.2.2. The upper portion, designated BNC (bottle neck with dropper insert and cap) of each bottle will be removed (cut off) using a ultrasonic cutting horn

8.2.2.2.3. The BNC will be discarded into a receptacle provided by the owner

8.2.2.2.4. This station will have the ability to be manually raised and lowered using a hand lead

screw to position the horn to accommodate different sizes of bottles.

8.2.2.2.5. The cap gripper portion of station 2 will have S/S tube as the support with S/S plates, the rotary actuator will have an anodized aluminum body, the two slide units will be anodized aluminum, with end plates and shafts S/S.

8.2.2.3. Station 3 - The remaining open bottle will then move (with no solution losses) and be picked up/rotated with contents poured into the Station 4 collection container provided, the bottle will then be discarded into a Station 3 collection container provided by the owner (note that the Station 2A and 3 discard collection containers can be the same). The third station supports will be S/S tube, with S/S plates for attachment of the slides. The rotary actuator will have an anodized body, the slides will have anodized bodies, S/S end plates and shafts, the wrist actuator and gripper will have anodized bodies, all fasteners will be S/S socket head, their will be an attaché stand to hold a vessel to pour the fluid into, a chute to guide the bottle into a container at the third station.

8.2.2.4. Station 4 – Collection container dedicated to each product collection and supplied by the production group. Container is a 20L standard glass carboy with standard top glass collection funnel.

8.3. Technical/ Usability Requirements

8.3.1. Agreed performance expectations are met, system is fit for use .

8.3.2. Performance – Downtime during use < 5%.

8.3.3. Safety – Zero injuries.

8.3.4. Ergonomics – Zero issues.

8.4. Environmental Requirements

System to continuously operate withtin a controlled ennvironment with the foloowing conditions:

8.4.1. Temperature – 61 deg F (+/- 5 deg F).

8.4.2. Humididty - < 60% RH.

8.4.3. Air Flow – Room air changes at > 50 per hour, uni-directional air flow at 50 – 110 lfpm.

8.4.4. Differentail Pressure of processing area at 0.050” WC positive to surrounding area.

8.4.5. Non-Viable Particulate Generaration at < 80 counts of particale size of 0.5 micron, zero counts allowable of 5 micron size.

8.4.6. Viable Particulate Generation – zero allowable.

8.5. Support Requirements

8.5.1. Preventive Maintenance (PM) – system and mechanic available for 3 hours every 6 months for system inpsection and PM.

8.5.2. Corrective Maintenance - mechanic available, on call, to respond to unplanned system adjustements and/or failures.

8.5.3. Calibration – system and technician available for 2 hours every 6 months for system calibration.

8.5.4. Engineering – engineering support avaialbel for operations support and continuouos improvement.

8.6. Billing Requirements

System is used interanlly and billed at actual to the requesting department.

9. Timelines and Milestones(M)

Note: timelines indicated include doumentation, are cumulative from baseline of T = 0 and are measured in man months, assuming no shortage of requireed resources.

9.1. (M) Authorization of Funding, T = 0

9.2. Engineering/Design Phase, T = 6

9.3. (M) Fabrication Phase, T = 18

9.4. (M) Verification and Validation Phase, T = 22

9.5. (M) Production Release, T = 23

10. Evaluation Plan and Performance Metrics

10.1. Evaluation Plan

With the current process baseline and performance characteristics known collect data for this new system then quantify data and compare/contrast with the manual process.

10.2. Performance Metrics

10.2.1. Product Sterility - zero analytical testing failures.

10.2.2. Cost of Operation less than current, manual process.

10.2.3. Cycle Time equal to or less than current, manual process.

10.2.4. Amount of Labor less than current, manual process.

A.3. Technical Risk and Avoidance

The following table lists the top ten technical risks, separated by general performance parameter, associated with this research.

ID#	Technical Risk	Avoidance Approach
Technology		
TR-1	Effectiveness of cutting plastic using ultrasonic's.	From vendor and industry, study engineering characteristics and performance of product. Design guidelines and analysis.
TR-2	Particulate (non-viable) generation into product during ultrasonic shearing of plastic.	Prototype testing and microscopic analysis.
TR-3	Product contamination (viable) of the system into the product causing sterility failure – disposal of product.	Prototype testing and microbial analysis seeking viable contaminants.
Performance/Reliability		
TR-4	System as a whole holding up to routine sanitization/cleaning with no deterioration or corrosion.	System specification via engineering, purchasing and material scientist's review of system materials and components with respect to compatibility with cleaning and sanitization chemicals, and methods.
TR-5	System performance as required without adversely effecting the	Application of good engineering practices, knowledge and experience

ID#	Technical Risk	Avoidance Approach
	controlled environment in which it operates.	with controlled environment requirements and monitoring
Safety		
TR-6	Risk to personnel ▪ System ergonomics ▪ Operating personnel ▪ Intervention during processing	Application of good human factors engineering in design. Involvement of operating personnel during design and fabrication. Prototype of key operator interface stations. (e.g. Control Panel) Failure mode analysis. Addition of energy isolation devices to cut-off sources during intervention <u>What to do – What NOT to do</u>! ▪ Documented standard operating procedure (SOP). ▪ Training of personnel for operations
Operational		
TR-7	System reliability - Ease of use, repeatability of system operation	FMEA Functional task analysis. Use cause and effect analysis. Accomplished in the verification and validation phase of testing. Active listening - Focus on communication with users and service personnel towards continuous system

ID#	Technical Risk	Avoidance Approach
		improvement.
TR-8	Will the system process all known packages	Engineering design for system format parts as change parts for different incoming bottles. Flexibility in accommodating future, yet unknown, packages.
TR-9	Service personnel ▪ Access ▪ Serviceability	Application of good engineering practices, knowledge and experience in design of system access an assurance that replacement parts are accessible. Prototype testing of service and repair tasks.
TR-10	Repair-ability	Effective documentation via a repair and maintenance plan. Define preventive maintenance program and procedures. Identify, define and maintain critical spare parts. Supplier evaluation. Create contact list for those parts which cannot be maintained in inventory, know what

ID#	Technical Risk	Avoidance Approach
		delivery lead times are and whom to contact. Train service personnel in mock up preventive and corrective maintenance tasks.

APPENDIX B

LITERATURE REVIEW

Vendors, U.S. Patents and Trademarks

Introduction - The following review of vendors and United States Patent Office issued patents or trademark is intended to asses the risk in terms of existing application of technology or potential litigation and/or competition to the proposed innovation.

"Benchmark" of this proposed innovation - Recall that this innovation specifically develops a system and method for emptying small volumes of liquid from individual bottles; more particularly, the innovation relates to an automated system and method for removing the tops from individual sealed bottles and pooling the small volumes of sterile liquid contained in each bottle together in a collection container while maintaining sterility of the liquid product.

Approach

- Ultrasonic Technology applied in aseptic processing

Process Application

- Pharmaceutical Industry
- Aseptic or sterile transfer of solutions (e.g. product), otherwise known as "product pooling".

Vendors(companies or providers)

Polar Process, Inc.

Description/Review

Located in New Hamburg, Ontario, Canada Polar Process, Inc. manufactures ultrasonic cutting systems not only to interface with there extruding and depositing equipment but also as free-standing units that can be added to your present process or conveyor line. We use only the very best Dukane Corporation ultrasonic generators, transducers, boosters and knives and we build complete integral systems around them
The systems we manufacture utilize either simple up and down movement for indexed systems, cam operated throws for medium linear speed product flow or fully integrated bi-axial servo motor control for high speed applications. Systems can be either cantilevered or gantry style dependent upon the width of the product to be cut.

Summary / Competitive Assessment

Competitive Assessment = **Low**

Company is based in Canada, is a system integrator and not application specific.

SUHR Cutters, A/S

Description/Review

Located in Biskop, Denmark, Suhr Cutters, A/S manufactures and supplies hot knife cutters, webbing cutters, strip cutting machines and length/strip cutters, guillotine cutters, automatic cutting equipment, ultrasonic cut, cut to length equipment, hole punchers and hole punching equipment, robe cutters, cutting equipment for narrow fabrics and webbing, hook and loop cutters, ultrasonic and ultrasonic cutters, prefeeds, prefeed device and slack-feeder, automatic marking equipment to provide cutting, punching, marking, printing in one process.

SUHR cutting systems are the result of 35 years experience in designing and manufacturing cutting systems. SUHR manufactures and supplies high-quality industrial cut-to-length equipment for narrow fabrics and other materials. They offer many types of automatic and manual cutting machines. Their equipment may be equipped to cut using a hot knife, guillotine,

or ultrasonic tooling. The offered cutting equipment can be used for many types of materials, including webbing, robe, tapes, cord, elastic, zipper, braid, tubing, film, hose, ribbon, hook & loop, bungee cord, safety harness, webbing, seat belts, zips, slings and Velcro.

Summary / Competitive Assessment

Competitive Assessment = **Low**.

Company is based in Denmark, is a system integrator and machine builder with applications not specific to pharmaceutical industry or sterile transfers.

Herrmann Ultrasonic

Description/Review

A global company with United States office in Schaumburg, Illinois, Herrmann Ultrasonics provides highly advanced technology and a variety of patented solutions for Ultrasonic Joining of thermoplastic parts. Their advertised "state-of-the-art" digital technology provides precise control of the welding process and ensures high-strength joints with repeated precision.

Herrmann's expertise covers a wide variety of different applications. Their specialists know exactly what it takes to achieve the best possible solution for Ultrasonic Welding Applications, such as a hermetic seal or the strongest possible joint between thermoplastic materials.

Summary / Competitive Assessment

Competitive Assessment = **Low**.

Company is a system integrator and machine builder with applications not specific to pharmaceutical industry or sterile transfers. Focus is on plastic joining and welding.

Branson Ultrasonic (Division of Emerson Industrial Automation)

Description/Review

With there United States office headquartered in Danbury, Connecticut, Branson claims to be the industry leader in the design, development, manufacture, and marketing of plastics joining, precision cleaning, ultrasonic processing, and ultrasonic metal welding equipment. Branson's global organization includes more than 1,800 employees and 70 sales and service offices throughout the world, Branson's technology and manufacturing facilities are in Connecticut, Michigan, New York, Canada, Mexico, Germany, Slovakia, China, Hong Kong, Japan, and Korea.

Summary / Competitive Assessment

Competitive Assessment = **Low**.

Company is a system integrator and machine builder with focus in plastics joining, precision cleaning, ultrasonic processing, and ultrasonic metal welding equipment not specific to pharmaceutical industry or sterile transfers.

Accusonics, Inc.

Description/Review

Located in Darien, Illinois, Accusonics sets itself apart by leading all independent acoustic tooling manufacturers in quality and delivery at affordable prices. Accusonics combines experience, knowledge, and applications expertise in order to meet the unique requirements of customers.
Customers parts and related applications are evaluated in their laboratory where they provide no-cost feasibility testing and troubleshooting associated with assembly problems and joint design recommendations.

Accusonics manufactures tooling per customers part files and machine specifications.

Summary / Competitive Assessment

Competitive Assessment = **Low**.
Company is a tooling manufacturer with focus on customer support and not application. No indication of any pharmaceutical industry experience.

Dukane Ultrasonics, Inc.

Description/Review

A global company with a United States based primarily in St. Charles, Illinois, Dukane is a provider of plastic assembly systems for the welding of thermoplastic materials. A standard line of ultrasonic, vibration, hot plate, spin welders, laser welders and thermal presses are used to provide solutions that meet the unique requirements of each customers application. The line also includes film and fabric sewing and slitting machines and custom automated assembly systems.

Dukane provides knowledgeable application engineers, no charge consultations, regional technical centers and a network of international offices. Dukane also offers a technical training program and extensive service and support.

Summary / Competitive Assessment

Competitive Assessment = **Low**.

Company is a core ultrasonic equipment/system manufacturer which offers customer application support and technical assistance with focus on equipment sales and customer support, not proprietary application. No indication of any pharmaceutical industry experience, specifically sterile transfer of solutions.

Sonobond Ultrasonics

Description/Review

Located in West Chester, Pennsylvania, Sonobond promotes innovation, performance, and service which make Sonobond the smart choice for ultrasonic welders. Sonobond Ultrasonics claims to be the internationally recognized leader in ultrasonic bonding for more than 45 years. In 1960, Sonobond (then known as Aeroprojects) received the first patent for ultrasonic metal welding. Since then, the company has received more than 150 additional patents. These include not only metal welders, but custom-engineered ultrasonic bonders of all types. Sonobond produces ultrasonic welding equipment for metal welding, textile bonding, plastic bonding, nonwoven bonding and filter assembly.

Sonobond claims state-of-the-art equipment which is dependable, durable, and easy to operate. Further claim that this is true whether you are using it for ultrasonic metal welding, ultrasonic plastic welding, for bonding nonwovens, or for another application.

Customers can purchase, rent, or lease Sonobond ultrasonic welders and bonders as stand-alone units or as modular systems for integration into customer's own production line or custom equipment. Sonobond's ultrasonic equipment is used by leading manufacturers in the automotive, appliance, filtration, HVAC, apparel, aerospace, security, medical, electronic, and electrical fields.

Summary / Competitive Assessment

Competitive Assessment = **Low**.

Company has many patents in ultrasonic's but they relate to welding, bonding and filter assembly. No indication of any plastic cutting or pharmaceutical industry experience, specifically sterile transfer of solutions.

FFR Ultrasonics, LTD.

Description/Review

Located in Queniborough, Leicestershire, in the UK (Europe), FFR Ultrasonics Ltd claims to be the UK's leading innovator in patented ultrasonic technology. A completely independent company, FFR offers the complete service in ultrasonic technology in the fields of plastic welding, cutting and fluidsonics (industrial sonochemistry or processing), with particular expertise in customer application development, R&D and consultancy.

FFR Ultrasonics Ltd was founded in 1985.

Dr Frank Rawson, FFR's innovator, has patented several unique ultrasonic processes giving FFR a position of prominence in leading ultrasonic innovation in Europe.

Summary / Competitive Assessment

Competitive Assessment = **Low**.

Company is based in the UK and has many patents in ultrasonic's but they relate to plastic welding, cutting and fluidsonics. No indication of any plastic cutting or pharmaceutical industry experience, specifically sterile transfer of solutions.

Patents

United States Patent Number: D418,395

Description/Review

Award Date: January 4, 2000
Search Response: Extruded *plastic* band for use in an *ultrasonic* tensioning, welding and *cutting* tool

Claims: The ornamental design for an extruded plastic band for use in an ultrasonic tensioning, welding and cutting tool, as shown and described.
Inventors:
Students; John J. (Collierville, TN); Wells, Jr.; Peter M. (Germantown, TN)
Assignee: Thomas & Betts International, Inc. (Sparks, NV)
Application No.: 081029
Filed: December 22, 1997

Summary / Competitive Assessment

Competitive Assessment = **Low**.

Thomas & Betts is a leading producer of connectors and components for worldwide electrical markets. The corporation manufactures its products on a worldwide basis, with manufacturing facilities throughout North America, in Europe and in the Far East. Distribution Centers are located in Byhalia, Mississippi; Bromont, Quebec; Sparks, Nevada; and LaLouviere, Belgium.

Patent relates specifically to a unique band for use in an ultrasonic tensioning, welding and cutting tool.

United States Patent Number: D415,672

Description/Review

Award Date: October 26, 1999

Search Response: Co-extruded plastic band for use in an ultrasonic tensioning, welding and cutting tool

Claims: The ornamental design for a co-extruded plastic band for use in an ultrasonic tensioning, welding and cutting tool, as shown and described.

Inventors:
Students; John J. (Collierville, TN); Wells, Jr.; Peter M. (Germantown, TN)
Assignee: Thomas & Betts International, Inc. (Sparks, NV)
Application. No.: 081030
Filed: December 22, 1997

Summary / Competitive Assessment

Competitive Assessment = **Low**.

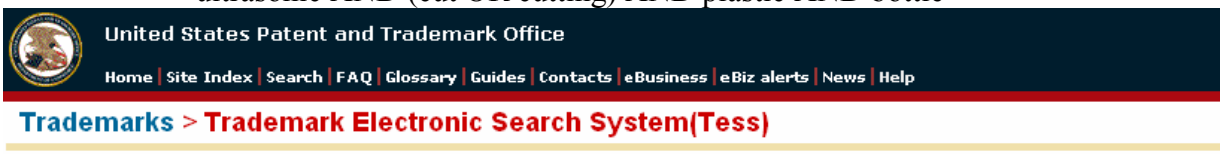
Thomas & Betts is a leading producer of connectors and components for worldwide electrical markets. The corporation manufactures its products on a worldwide basis, with manufacturing facilities throughout North America, in Europe and in the Far East. Distribution Centers are located in Byhalia, Mississippi; Bromont, Quebec; Sparks, Nevada; and LaLouviere, Belgium.

Patent relates specifically to a unique band for use in an ultrasonic tensioning, welding and cutting tool.

Trademarks

Using the following search criteria, including plurals:

"ultrasonic AND (cut OR cutting) AND plastic AND bottle"



22 potential trademarks were reported as follows…

	Serial Number	Reg. Number	Word Mark	Check Status	Live/Dead
1	78189691		YELLO	TARR	DEAD
2	78437182		EBARA	TARR	LIVE
3	78437126			TARR	LIVE
4	78646810		PYROPHILIC	TARR	LIVE
5	78646758		PYROBE	TARR	LIVE
6	76379549	2909472	LT-CI	TARR	LIVE
7	76517322		TM	TARR	LIVE
8	76133905		FUTURE	TARR	LIVE
9	76585316		FUTURISTIC	TARR	LIVE
10	76379548	2878300	LTS-CI	TARR	LIVE
11	76632679		!30 130TH ANNIVERSARY	TARR	LIVE
12	76289767		DIPOLGY	TARR	LIVE
13	75328083	2391863	MAXCESS INTERNATIONAL	TARR	LIVE
14	75598237	2849974	VW	TARR	LIVE
15	75598249	2835662	VOLKSWAGEN	TARR	LIVE
16	75355935	2568757	PFU	TARR	LIVE
17	75429152			TARR	DEAD
18	75328082		MAXCESS AUTOMATION	TARR	DEAD
19	75191528	2409698	DENSO	TARR	LIVE
20	74694369	2241416	EXPO2000 HANNOVER	TARR	LIVE
21	74066232		DANFOSS AUTOMATIC CONTROL HOUSE	TARR	DEAD
22	73799683		AUTOMATIC CONTROL HOUSE	TARR	DEAD

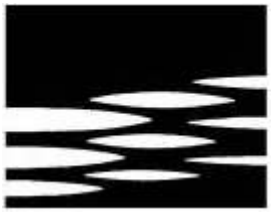
Review of the finding above shows numbers 1, 17, 18, 21 and 24 to be “DEAD” or inactive, focus of this analysis is on those indicated as “LIVE” by the trademark office.

Trademark Serial Number 78437182

Word Mark	EBARA
Translations	The foreign wording in the mark translates into English as SESAME FIELD.
Goods and Services	
Mark Drawing Code	(5) WORDS, LETTERS, AND/OR NUMBERS IN STYLIZED FORM
Serial Number	78437182
Filing Date	June 17, 2004
Current Filing Basis	1B;44D

Original Filing Basis	1B;44D
Owner	(APPLICANT) Ebara Corporation JAPAN 11-1, Haneda Asahi-cho Ota-ku, Tokyo JAPAN
Attorney of Record	Lawrence E. Abelman
Priority Date	December 19, 2003
Prior Registrations	1010099;1397397;1749807;AND OTHERS
Description of Mark	The mark consists of the word EBARA in special form.
Type of Mark	TRADEMARK. SERVICE MARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 78437126

Mark Drawing Code	 (2) DESIGN ONLY{trademarked symbol}
Design Search Code	260302 260313 261121
Serial Number	78437126
Filing Date	June 17, 2004

Current Filing Basis	1B
Original Filing Basis	1B;44D
Owner	(APPLICANT) Ebara Corporation JAPAN 11-1, Haneda Asahi-cho Ota-ku Tokyo JAPAN
Attorney of Record	Lawrence E. Abelman
Priority Date	December 19, 2003
Prior Registrations	1397397;2904077
Description of Mark	The mark consists of a series of interlocking elongated oval shapes.
Type of Mark	TRADEMARK. SERVICE MARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 78646810

Word Mark	PYROPHILIC
Goods and Services	
Standard Characters Claimed	
Mark Drawing Code	(4) STANDARD CHARACTER MARK
Serial Number	78646810
Filing Date	June 8, 2005
Current Filing	1B

Basis	
Original Filing Basis	1B
Owner	(APPLICANT) Terra Preta, LLC John C. Marrelli, a United States Citizen LTD LIAB CO DELAWARE 3501 Silverside Road - Naaman's Building , Suite 206; Wilmington DELAWARE 19810
Attorney of Record	Bruce Rosen
Type of Mark	TRADEMARK. SERVICE MARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 78646758

Word Mark	PYROBE
Goods and Services	Pasta and cake, Bakery desserts, Bakery goods, Bakery products,
Standard Characters Claimed	
Mark Drawing Code	(4) STANDARD CHARACTER MARK
Serial Number	78646758
Filing Date	June 8, 2005
Current Filing Basis	1B
Original	1B

Filing Basis	
Owner	(APPLICANT) Terra Preta, LLC John C. Marrelli, United States Citizen LTD LIAB CO DELAWARE 3501 Silverside Road-Naaman's Building, Suite 206; Wilimington DELAWARE 19810
Attorney of Record	Bruce Rosen
Type of Mark	TRADEMARK. SERVICE MARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 76379549, Registration Number 2909472

Word Mark	LT-CI
Goods and Services	IC 007. US 013 019 021 023 031 034 035. G & S: MACHINES AND MACHINE TOOLS, NAMELY, MANUFACTURING MACHINES, ASSEMBLING MACHINES, MANIPULATION MACHINES, JOINING MACHINES, YOKE MACHINES, MACHINE PARTS IN THE NATURE OF WORK FIXTURES AND WORK PIECE CARRIERS.
Mark Drawing Code	(1) TYPED DRAWING
Serial Number	76379549
Filing Date	March 7, 2002
Current Filing Basis	44E
Original Filing Basis	1B;44D;44E

Published for Opposition	September 21, 2004
Change In Registration	CHANGE IN REGISTRATION HAS OCCURRED
Registration Number	2909472
Registration Date	December 14, 2004
Owner	(REGISTRANT) STICHT, WALTER INDIVIDUAL AUSTRIA Karl-Heinrich-Waggerl-Strasse 8 4800 Attnang-Puchheim AUSTRIA
Attorney of Record	Stewart J. Bellus
Priority Date	November 15, 2001
Type of Mark	TRADEMARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 76517322

Word Mark	TM
Goods and Services	Ear plugs, not for medical purposes; electric arc welders; batteries; egg-candlers; cash registers; coin counting and sorting machines; light emitting diode displays; photocopying machines; abacuses; time and date stamping machines; time clocks, namely, time recording devices; voting machines; postage stamp checking apparatus, namely scanners; vending machines; metered gasoline pumps; coin-operated gates for car parking facilities; life nets; life belts; life jackets; life buoys; fire extinguishers; fire hose nozzles; sprinkler systems for fire protection; fire alarms; carbon monoxide gas alarms; natural gas alarms; theft alarms; protective helmets; railway signals; vehicle breakdown

	warning triangles; luminous or mechanical road signs; electric door openers; vehicle drive training simulators; sports training simulators; air-gas producers; constant temperature incubators; constant humidity incubators; glassware for scientific experiments in laboratories; porcelain ware for scientific experiments in laboratories; furnaces for laboratory experiments; automatic liquid-level control machines and instruments; automatic temperature control machines and instruments; automatic combustion control machines and instruments; automatic vacuum control machines and instruments; program control machines and instruments; metal compression testing machines; metal hardness testing machines;
Mark Drawing Code	(5) WORDS, LETTERS, AND/OR NUMBERS IN STYLIZED FORM
Serial Number	76517322
Filing Date	May 23, 2003
Current Filing Basis	44E
Original Filing Basis	1B;44D
Owner	(APPLICANT) Toshiba Matsushita Display Technology Co., Ltd. CORPORATION JAPAN 1-8, Kounan 4-chome, Minato-ku Tokyo JAPAN
Attorney of Record	CHRISTINA J. HIEBER
Priority Date	November 29, 2002
Type of Mark	TRADEMARK. SERVICE MARK
Register	PRINCIPAL

Live/Dead Indicator	LIVE

Trademark Serial Number 76133905

Word Mark	FUTURE
Goods and Services	Adhesives, glues, abrasives, absorbing carbons, adjutants, agar alcohol, antifreeze, anti static spray for clothing and for electronic equipment, automotive brake systems leak sealant, automotive rust inhibitors tire inflator sealers, bio chemicals, Battery, botanical extracts for use in making cosmetics, brake fluid, catalysts for use in manufacturing of industrial chemicals and rubber processing industry; cells for scientific, laboratory or medical research; chemical additives for use in the manufacturing of food, pharmaceuticals, cosmetics and a wide variety of goods; Games and playthings; namely, (specify- the common commercial names of the goods); gymnastic and sporting articles, namely, (specify the common commercial names of the -goods; Christmas tree decorations;A-mend to include toys dolls, toy action figures, stuffed toys, plush toys, bend able toys, mechanical toys, inflatable toys, electronic toys, board games, card games, hand held units for playing electronic games, arcade games, infant toys, -sand toys, ride on toys, radio controlled toys vehicles, sketching toys, stuffed toy animals, -toy cooking ware, clothing pop up toys, so-ft, toys, water toys, construction toys, wind up toys, action skilled games, pails, playthings, balloons, toy candy dispensers and holder, toy vehicles, stand alone video game machine, hi bounce balls, costume masks, paper face masks, toy model vehicles and related accessories there of sold as units, toy pedal cars, play sets for action fighters, play sets for toy vehicles, skateboards, dimensional puzzles, toy ba MEAT, FISH POULTRY AND GAME MEAT EXTRACTS, PRESERVED, DRIED, AND COOKED FRUITS, VEGETABLES, JELLIES, JAMS, FRUIT SAUCES, EGGS, MILK, MILK PRODUCTS, EDIBLE OILS AND FATS COFFEE, TEA, COCOA, SUGAR, RICE, TAPIOCA, SAGO, ARTIFICIAL COFFEE FLOUR AND PREPARATIONS MADE

	FORM CEREALS BREAD, PASTRY, AND CONFECTIONERY, HONEY, TREACLE, YEAST, BACKING POWDER, SALT, MUSTARD, VINEGAR, SAUCES CONDIMENTS SPICES, ICE AGRICULTURAL HORTICULTURAL AND FORESTRY PRODUCTS AND GRAINS NOT INCLUDED IN OTHER CLASSES, LIVE ANIMALS, FRESH FRUITS, VEGETABLES SEEDS NATURAL PLANTS AND FLOWERS, FOODSTUFFS, FOR ANIMALS, MALT
Mark Drawing Code	(1) TYPED DRAWING
Serial Number	76133905
Filing Date	September 22, 2000
Current Filing Basis	1B
Original Filing Basis	1B
Owner	(APPLICANT) ANDERSON, KENT G INDIVIDUAL UNITED STATES 925 N GRIFFIN BISMARCK NORTH DAKOTA 58501
Attorney of Record	Paul E. Fahrenkopf
Type of Mark	TRADEMARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 76585316

Word Mark	FUTURISTIC

Goods and Services	Rops , Strings, Nets ,Tents Camping Gear , Awinings, Sails, Sacks, Bags, Padding ,Stuffing Materials, Rubber ,Plastics, materials Used In Industry chemicals used in industry, science and photography, as well as in agriculture, horticulture and forestry-- Bleaching preparations and other substance for laundry use Industrial oils and general purposes greases, all purpose lubricants petroleum based dust absorbing compositions for use in (indicate purpose , e;g; road building , sweep , dust laying), Pharmaceutical , veterinary and sanitary preparations , namely (specify the common commercial names of the goods) Common metals and their alloys in the form of coils; strip or sheet ; metal strip; metal building materials, namely Instruments apparatus for recording transmission or reproduction of sound or images Advertising, Marketing ,Business Management, Business administration Office Functions; Manufacturing representatives, independent sales representatives, sales services ;Marketing, Distributing Etc Of New Products And Servcies There Of Insurance, Financial affairs, Monetary affairs, real estate affairs Building construction, repair, installation services, Telecommunications Education, Providing of training, entertainment, sporting n cultural activities
Mark Drawing Code	(5) WORDS, LETTERS, AND/OR NUMBERS IN STYLIZED FORM
Serial Number	76585316

Filing Date	April 6, 2004
Current Filing Basis	1B
Original Filing Basis	1B
Owner	(APPLICANT) ANDERSON, KENT G INDIVIDUAL UNITED STATES FUTURE SMITH 925 N GRIFFIN BISMARCK NORTH DAKOTA 58501
Type of Mark	TRADEMARK. SERVICE MARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 76379548, Registration Number 2878300

Word Mark	LTS-CI
Goods and Services	MACHINES AND MACHINE TOOLS, NAMELY, MANUFACTURING MACHINES, ASSEMBLING MACHINES, MANIPULATION MACHINES, JOINING MACHINES, INJECTION PLASTIC MOLDING MACHINES, WELDING MACHINES, QUALITY CONTROL MACHINES FOR MONITORING ASSEMBLY AND PROCESSING WORK
Mark Drawing Code	(1) TYPED DRAWING
Serial Number	76379548
Filing Date	March 7, 2002
Current Filing Basis	44E

Original Filing Basis	1B;44D;44E
Published for Opposition	June 8, 2004
Change In Registration	CHANGE IN REGISTRATION HAS OCCURRED
Registration Number	2878300
Registration Date	August 31, 2004
Owner	(REGISTRANT) Sticht, Walter INDIVIDUAL AUSTRIA Karl-Heinrich-Waggerl-Strasse 8 4800 Attnang-Puchheim AUSTRIA
Attorney of Record	STEWART J. BELLUS
Priority Date	November 15, 2001
Type of Mark	TRADEMARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 76632679

Word Mark	!30 130TH ANNIVERSARY
Goods and	Turbines; boilers for turbines; hydroelectric generating installations; thermal electric generating installations; diesel-electric generating

Services	installations; electric mixers and blenders
Mark Drawing Code	(5) WORDS, LETTERS, AND/OR NUMBERS IN STYLIZED FORM
Serial Number	76632679
Filing Date	March 3, 2005
Current Filing Basis	1B;44D
Original Filing Basis	1B;44D
Owner	(APPLICANT) Kabushiki Kaisha Toshiba TA Toshiba Corporation CORPORATION JAPAN 1-1, Shibaura 1-chome Minato-ku, Tokyo JAPAN
Attorney of Record	Brian E. Banner
Priority Date	November 30, 2004
Type of Mark	TRADEMARK. SERVICE MARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 76289767

Word Mark	DIPOLGY
Goods and Services	Physical and chemical apparatus and instruments, namely air-gas generators and experimental furnaces; measuring apparatus and instruments, namely thermometers, gas meters, water meters, pressure meters, acoustic meters, tachometers, accelerometers, vibration gauges, sound meters, speedometers, flow meters; automatic pressure control apparatus; automatic flow control apparatus; metal compression testing

	apparatus; concrete testing apparatus; electrical distribution or control machines
Mark Drawing Code	(1) TYPED DRAWING
Serial Number	76289767
Filing Date	July 23, 2001
Current Filing Basis	1B;44D
Original Filing Basis	44D
Owner	(APPLICANT) CCI KABUSHIKI KAISHA DBA CCI Corporation CORPORATION JAPAN 12, Shin-hazama Seki-shi, 501-3923 JAPAN
Attorney of Record	ROBERT G. SHEPHERD
Priority Date	January 22, 2001
Type of Mark	TRADEMARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 75328083, Registration Number 2391863

Word Mark	MAXCESS INTERNATIONAL
Goods and Services	Linear actuators comprising motors, belts, ball screws and nuts, hydraulic reservoir assemblies comprising motors, hydraulic pumps, relief valves and plumbing, and hydraulic servo control valves, all

	used to move and laterally position webs or strips of metal, paper, paperboard, corrugated paper products, cardboard, plastic, rubber or textiles so that they may be printed with one or more colors, or cut or slit, or surface treated or measured Installation, maintenance and repair services in the field of process control systems, drive systems, guiding systems, positioning systems, tensioning systems, winding systems, cutting and slitting systems, materials handling systems, brake systems, clutch systems, automatic quality control, defect detection and inspection systems, measuring systems, imaging and recording systems and control systems. FIRST USE: 19991015. FIRST USE IN COMMERCE: 19991015 Consultation and advisory services in the field of design, manufacturing, installation, maintenance and repair of process control systems, dirve systems, guiding systems, positioning systems, tensioning system, winding systems, cutting and slitting systems, material handling systems, brake systems, clutch systems, automatic quality control, defect detection and inspection systems, measuring systems, imaging and recording systems, and control systems. FIRST USE: 19991015. FIRST USE IN COMMERCE: 19991015
Mark Drawing Code	(1) TYPED DRAWING
Serial Number	75328083
Filing Date	July 21, 1997
Current Filing Basis	1A
Original Filing Basis	1B
Published for Opposition	June 8, 1999

Registration Number	2391863
Registration Date	October 3, 2000
Owner	(REGISTRANT) MAXCESS INTERNATIONAL CORPORATION CORPORATION DELAWARE 101 FEDERAL STREET SUITE 1900 BOSTON MASSACHUSETTS 02110
Assignment Recorded	ASSIGNMENT RECORDED
Attorney of Record	DAVID P SHARROW
Disclaimer	NO CLAIM IS MADE TO THE EXCLUSIVE RIGHT TO USE "INTERNATIONAL" APART FROM THE MARK AS SHOWN
Type of Mark	TRADEMARK. SERVICE MARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 75598237, Registration Number 2849974

Word Mark	VW
Goods and Services	CHEMICALS USED IN INDUSTRY, SCIENCE, PHOTOGRAPHY, HORTICULTURE AND FORESTRY, NAMELY, CATALYSTS; CHLORINE, MINERAL FILTERING MATERIALS, UNPROCESSED CELLULOSE; CHEMICALS FOR USE IN THE MANUFACTURE OF LACQUERS, ANTI-RUST PREPARATIONS, PAINTS, ADHESIVES, COSMETICS; UNPROCESSED ARTIFICIAL RESINS FOR USE IN THE

	MANUFACTURE OF VEHICLES, MACHINES, AND ELECTROTECHNICAL ARTICLES
Mark Drawing Code	(3) DESIGN PLUS WORDS, LETTERS, AND/OR NUMBERS
Design Search Code	260101
Serial Number	75598237
Filing Date	December 2, 1998
Current Filing Basis	44E
Original Filing Basis	44E
Published for Opposition	October 15, 2002
Registration Number	2849974
Registration Date	June 8, 2004
Owner	(REGISTRANT) Volkswagen Aktiengesellschaft CORPORATION FED REP GERMANY D-38436 Wolfsburg FED REP GERMANY
Attorney of Record	Barth X. deRosa
Prior Registrations	0617131;0790621;0808381;0819297;1367556;1378042;AND OTHERS
Type of Mark	TRADEMARK. SERVICE MARK

Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 75598249, Registration Number 2835662

Word Mark	VOLKSWAGEN
Goods and Services	CHEMICALS USED IN INDUSTRY, SCIENCE, PHOTOGRAPHY, HORTICULTURE AND FORESTRY, NAMELY, CATALYSTS; CHLORINE, MINERAL FILTERING MATERIALS, UNPROCESSED CELLULOSE; CHEMICALS FOR USE IN THE MANUFACTURE OF LACQUERS, ANTI-RUST PREPARATIONS, PAINTS, ADHESIVES, COSMETICS; UNPROCESSED ARTIFICIAL RESINS FOR USE IN THE MANUFACTURE OF VEHICLES, MACHINES, AND ELECTROTECHNICAL ARTICLES; UNPROCESSED ARTIFICIAL RESINS FOR USE IN THE VEHICLE
Mark Drawing Code	(1) TYPED DRAWING
Serial Number	75598249
Filing Date	December 2, 1998
Current Filing Basis	44E
Original Filing Basis	44E
Published for Opposition	October 15, 2002
Registration Number	2835662
Registration	April 27, 2004

Date	
Owner	(REGISTRANT) Volkswagen Aktiengesellschaft CORPORATION FED REP GERMANY D-38436 Wolfsburg FED REP GERMANY
Attorney of Record	Barth X. deRosa
Prior Registrations	0617131;0790621;0808381;0819297;1367556;1378042;AND OTHERS
Type of Mark	TRADEMARK. SERVICE MARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 75355935, Registration Number 2568757

Word Mark	PFU
Goods and Services	physical or chemical scales and weighing scales; rulers; electrical distribution controls; batteries; electric or magnetic measuring machines and instruments; electric wires and cables; photographic cameras; cinematographic cameras; lenses; life saving jackets and preservers; telephone sets; telegraphs;facsimile machines; prerecorded records; computers, computer peripherals, computer operating programs, namely operating software, middleware software, application software and basic software for running other programs; data processing apparatus and instruments
Mark Drawing Code	(3) DESIGN PLUS WORDS, LETTERS, AND/OR NUMBERS
Design	260521 261127 270301

Search Code	
Serial Number	75355935
Filing Date	September 10, 1997
Current Filing Basis	44E
Original Filing Basis	1B;44D
Published for Opposition	November 14, 2000
Change In Registration	CHANGE IN REGISTRATION HAS OCCURRED
Registration Number	2568757
Registration Date	May 14, 2002
Owner	(REGISTRANT) Kabushiki Kaisha PFU (PFU LIMITED) CORPORATION JAPAN Aza Unoke Nu 98-2, Unoke-machi Kahoku-gun Ishikawa-kun JAPAN
Attorney of Record	CURTIS B HAMRE
Description of Mark	The mark consists of the letters "PFU" and a triangle design. The lining shown in the drawing is a feature of the mark and is not intended to indicate color.
Type of Mark	TRADEMARK. COLLECTIVE TRADEMARK. SERVICE MARK. COLLECTIVE SERVICE MARK
Register	PRINCIPAL
Live/Dead	LIVE

Indicator	

Trademark Serial Number 75191528, Registration Number 2409698

Word Mark	DENSO
Goods and Services	anti-freeze for engines; antiknock substances for internal combustion; engine decarbonizing chemicals; detergent additives to gasoline and brake fluids; refrigerants all purpose cleaning preparations; perfumes; skin soaps; radiator cleaning liquids and windscreen cleaning liquids non-chemical additives to motor fuel; industrial grease; industrial oil; industrial lubricants; industrial lubricating grease; industrial lubricating oil; and motor fuel for diesel and gasoline engines air freshening preparation; air purifying preparation and deodorants (other than for personal use); air fresheners for vehicle compartment use ducts of metal for ventilating and air conditioning installations; foundry molds of metal and metal skid chains alternators for land vehicles hand instruments and hand tools, namely, abrading instruments Electric relays; voltage regulator; power antennas; electric buzzers; warning alarms for vehicle condition; transceivers; telephone apparatus Resins in bars, blocks and sheets for general industrial use; semi-processed brake lining materials; clutch linings; compressed air pipe fittings not of metal; cylinder jointings; plastic film for commercial and industrial packing use; pipe gaskets; and rubber bottle stoppers
Mark Drawing Code	(1) TYPED DRAWING

Serial Number	75191528
Filing Date	October 28, 1996
Current Filing Basis	44E
Original Filing Basis	1B
Published for Opposition	September 12, 2000
Registration Number	2409698
Registration Date	December 5, 2000
Owner	(REGISTRANT) Denso Corporation CORPORATION JAPAN 1-1 Showa-Cho Kariya-City Aichi-Pref JAPAN
Attorney of Record	PAUL W KRUSE
Priority Date	April 23, 1996
Prior Registrations	1075835;1393123
Type of Mark	TRADEMARK. SERVICE MARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Trademark Serial Number 74694369, Registration Number 2241416

Word Mark	EXPO2000 HANNOVER

Goods and Services	meat, fish, poultry, game; meat extracts; preserved, dried and cooked fruit and vegetables (excluding ice cream); edible oils and fats; ready-to-serve meals, ready-to-serve frozen washing and bleaching agents for laundry; cleaning, polishing, degreasing agents; metal washing creams; body soaps; perfumes and body oils; creams, lotions, shampoos, shower baths, bath salts, hair treatment liquids, cosmetics all purpose lubricants; dust-absorbing, dust-moistening and dust bonding agents for use on unpaved roads; gaseous, liquid and solid fuels, namely, engine fuels; luminous matter, namely, lamp oil, kerosene, methylated spirits; candles, wicks physical, chemical, optical, photographic, nautical and geodetic equipment, devices and instruments; weighing, signalling, measuring, counting, and recording devices, closed-loop control devices and switchgear; electrical switchgear and control cabinets, lamps and luminaires and their components; specular reflectors for lighting fixtures; portable electric heaters; infrared lamps
Mark Drawing Code	(3) DESIGN PLUS WORDS, LETTERS, AND/OR NUMBERS
Design Search Code	261703
Serial Number	74694369
Filing Date	June 27, 1995
Current Filing Basis	44E
Original Filing Basis	1B;44D

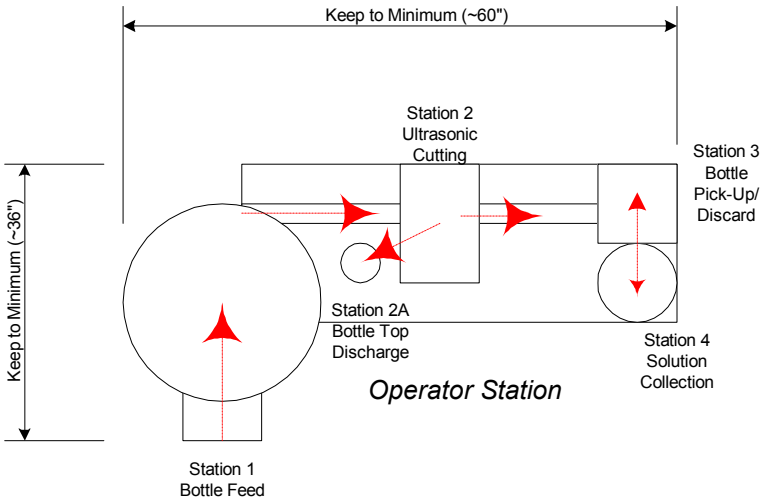
Published for Opposition	November 24, 1998
Registration Number	2241416
Registration Date	April 27, 1999
Owner	(REGISTRANT) Gesellschaft zur Vorbereitung und Durchfuhrung der Weltausstellung EXPO 2000 in Hannover mbH CORPORATION FED REP GERMANY Thurnithistrasse 2 D-30519 Hannover FED REP GERMANY
Attorney of Record	Lawrence E. Abelman
Priority Date	March 27, 1995
Disclaimer	NO CLAIM IS MADE TO THE EXCLUSIVE RIGHT TO USE "HANNOVER" APART FROM THE MARK AS SHOWN
Type of Mark	TRADEMARK. SERVICE MARK
Register	PRINCIPAL
Live/Dead Indicator	LIVE

Summary/Conclusion
A thorough review and analysis has been completed as related to this research. All competitive risks are defined at a “Low” level. Trademark review indicated no areas of duplication specific to the sterile transfer of solution within the pharmaceutical industry. With the minimal risks identified, the recommendation is to proceed with this system and method research, innovation, development and implementation.

APPENDIX C

BID SPECIFICATION

Objective: Fabricate a safe, ergonomic, automated portable machine, suitable for use in an aseptic environment, for the purpose of removing the cap, dropper insert, and upper neck off a plastic eyedropper type bottle, pour the fluid into a secondary collection container for future use, and discard the bottle, cap and insert from which the solution originated into a collection container.



Functional Discussion, reference plan view above:

1. The machine is viewed as an "in-line", station to station, machine.
2. Machine is of stainless steel and plastic, cleanable/sanitizable construction, capable of being sprayed or wiped with cleaning solution

3. comprising paracetic acid at 0.08% by weight, acetic acid at <10% by weight and hydrogen peroxide at 1.0% by weight.
4. Machine will operate continuously within a controlled environment not generating non-viable particles at counts >29 of 5.0 particle size and 3,520 of 0.5 particle size.
5. Target average cycle time for a full cycle is eleven (11) seconds, allowing for five (5) bottles per min. with a maximum of (8) seconds per cycle or (7) bottles per min.
6. Electrical to be minimum NEMA 4 rated using 129 volt, single phase, 20 amp, electrical supply.
7. Overall machine control architecture to be Allen-Bradley® PLC based.
8. Compressed air pressure available at 90 psi, clean and dry.
9. Footprint of the machine will be approximately 5 feet by 3 feet, portable with "clean room" casters (stainless steel, non-marking), two fixed, two swivel, all with locks.
10. Machine base will have one stainless steel perforated shelve, enclosed with Lexan® panels, to hold the ultrasonic power supply, air supply manifold and air exhaust manifold.
11. Machine is planned to require one (1) scientist for operation.
12. Station 1 - Bottles will be placed by an operator onto a rotary feed table which in turn feeds a conveyor serving as staging for Station 2

13. Station 2 - Ultrasonics, with a wash-down style transducer with air cooling, stainless steel booster, and a knife edge horn, mounted to an air slide.
14. Varying height and diameter of labeled round or oval bottles, or group of bottles, will be picked up or otherwise stopped or presented to the ultrasonic cutting station
15. The upper portion, designated BNC (bottle neck with dropper insert and cap) of each bottle will be removed (cut off) using a ultrasonic cutting horn
16. The BNC will be discarded into a receptacle provided by the owner
17. This station will have the ability to be manually raised and lowered using a hand lead screw to position the horn to accommodate different sizes of bottles.
18. The cap gripper portion of station 2 will have S/S tube as the support with S/S plates, the rotary actuator will have an anodized aluminum body, the two slide units will be anodized aluminum, with end plates and shafts S/S.
19. Station 3 - The remaining open bottle will then move (with no solution losses) and be picked up/rotated with contents poured into the Station 4 collection container provided by the owner, the bottle will then be discarded into a Station 3 collection container provided by the owner

(note that the Station 2A and 3 discard collection containers can be the same). The third station supports will be S/S tube, with S/S plates for attachment of the slides. The rotary actuator will have an anodized body, the slides will have anodized bodies, S/S end plates and shafts, the wrist actuator and gripper will have anodized bodies, all fasteners will be S/S socket head, their will be an attaché stand to hold a vessel to pour the fluid into, a chute to guide the bottle into a container at the third station.

20. Safety - The machine will be equipped with light beam barriers, or equal, as needed for operator safety. Any additional safety equipment required will be provided by the purchaser, or added to the quote price.

APPENDIX D

RAW DATA

D.1. Max Data from Collected Raw Data

LDPE (oval) MAX Data			LDPE (round-clear) MAX Data		
Cycle #	MAX Energy (Joules)	MAX Power (Watts)	Cycle #	MAX Energy (Joules)	MAX Power (Watts)
1	254	150	1	251	77
2	254	149	2	136	78
3	254	156	3	249	79
4	253	156	4	243	80
5	247	156	5	248	81
6	254	156	6	239	80
7	254	151	7	239	81
8	254	157	8	244	79
9	254	157	9	241	79
10	253	158	10	244	78
11	145	158	11	243	79
12	249	158	12	252	79
13	249	127	13	241	80
14	254	160	14	243	79
15	249	160	15	243	79
16	254	152	16	244	80
17	247	144	17	239	80
18	251	159	18	239	79
19	248	136	19	254	80
20	251	159	20	246	80
21	254	149	21	254	78
22	252	157	22	254	79
23	254	157	23	238	79
24	254	158	24	240	79
25	251	158	25	237	80
26	252	145	26	239	79
27	247	156	27	240	80
28	254	153	28	254	78
29	247	139	29	251	78
30	254	150	30	249	77
31	254	148	31	249	78
32	254	147	32	254	79
33	254	147	33	243	79

34	254	141	34	236	78
35	250	144	35	239	78
36	254	141	36	254	77
37	246	107	37	254	79
38	254	139	38	239	79
39	253	137	39	246	79
40	254	137	40	254	77
41	252	137	41	248	79
42	254	128	42	253	79
43	195	134	43	244	79
44	254	134	44	253	79
45	254	107	45	242	77
46	252	134	46	238	78
47	254	133	47	254	79
48	254	130	48	254	77
49	252	128	49	247	79
50	254	104	50	240	79
51	254	128	51	254	77
52	247	127	52	240	79
53	252	109	53	243	77
54	254	126	54	254	77
55	254	123	55	248	78
56	249	122	56	243	77
57	248	120	57	247	78
58	245	100	58	241	77
59	253	115	59	173	79
60	251	107	60	250	79
61	249	106	61	254	81
62	253	115	62	242	79
63	249	106	63	238	79
64	254	115	64	254	77
65	165	106	65	252	78
66	250	99	66	249	79
67	253	106	67	253	78
68	252	113	68	238	78
69	254	106	69	233	77
70	242	105	70	243	78
71	127	106	71	250	78
72	254	113	72	252	77
73	254	105	73	237	79
74	248	98	74	246	78
75	251	104	75	138	77
76	254	104	76	242	77
77	254	104	77	246	78
78	248	104	78	238	77

79	250	104	79	242	78
80	254	104	80	254	77
81	248	104	81	254	78
82	236	97	82	140	77
83	244	103	83	254	77
84	249	104	84	199	78
85	250	103	85	254	78
86	251	104	86	239	78
87	247	103	87	253	77
88	254	104	88	249	79
89	253	104	89	236	78
90	251	98	90	243	79
91	247	104	91	249	77
92	253	104	92	251	79
93	182	113	93	132	76
94	254	104	94	243	77
95	251	103	95	240	78
96	251	104	96	244	76
97	254	104	97	137	78
98	254	98	98	254	77
99	214	104	99	245	78
100	252	103	100	236	78
101	244	103	101	250	78
102	254	103	102	244	77
103	246	102	103	247	78
104	254	114	104	253	77
105	252	102	105	252	78
106	193	97	106	239	78
107	180	102	107	254	79
108	246	102	108	240	78
109	254	102	109	237	78
110	254	102	110	254	79
111	245	95	111	246	78
112	247	102	112	238	77
113	248	101	113	254	79
114	206	102	114	244	77
115	251	102	115	254	76
116	253	102	116	247	77
117	244	102	117	179	77
118	246	102	118	253	78
119	242	96	119	241	78
120	248	102	120	181	77
121	242	102	121	244	78
122	248	102	122	248	78
123	241	102	123	226	78

124	250	102	124	235	77
125	169	102	125	254	78
126	182	102	126	243	78
127	251	97	127	254	78
128	247	102	128	227	78
129	251	102	129	214	78
130	212	103	130	254	78
131	249	102	131	244	78
132	250	98	132	247	78
133	248	103	133	236	78
134	189	102	134	235	77
135	252	99	135	254	78
136	251	102	136	150	78
137	254	102	137	244	78
138	239	103	138	251	79
139	244	138	139	241	77
140	247	135	140	250	76
141	247	136	141	245	77
142	123	102	142	219	77
143	254	102	143	243	77
144	249	102	144	241	77
145	243	101	145	212	77
146	254	102	146	236	78
147	208	102	147	217	78
148	245	98			
149	203	103			
150	247	113			
151	250	103			
152	251	102			
153	244	95			
154	243	102			
155	249	102			
156	254	103			
157	249	102			
158	241	103			
159	243	103			
160	253	113			
161	240	96			
162	236	102			
163	245	102			
164	173	97			
165	144	101			
166	245	101			
167	253	101			
168	242	101			

169	253	95
170	243	101
171	251	101
172	253	102
173	247	101
174	248	101
175	155	101
176	254	102
177	243	94
178	245	101
179	145	101
180	250	97
181	248	101
182	135	101
183	253	101
184	252	95
185	246	101
186	241	101
187	250	96
188	226	101
189	246	101
190	249	101
191	252	101
192	249	100
193	239	100
194	125	100
195	254	96
196	243	101
197	249	101
199	230	101
200	231	101
201	223	99

SPP (oval-clear) MAX Data			PET (round-white) MAX Data		
Cycle #	MAX Energy (Joules)	MAX Power (Watts)	Cycle #	MAX Energy (Joules)	MAX Power (Watts)
1	247	147	1	245	79
2	247	148	2	248	80
3	252	148	3	241	87
4	254	149	4	254	88
5	248	149	5	250	90
6	244	149	6	245	91
7	254	148	7	254	96
8	249	143	8	249	100
9	254	149	9	254	96
10	254	149	10	226	98
11	247	149	11	249	98
12	247	149	12	253	97
13	254	150	13	251	97
14	254	150	14	250	100
15	249	150	15	247	98
16	254	151	16	251	102
17	253	139	17	246	106
18	254	153	18	249	105
19	140	146	19	244	109
20	252	148	20	241	106
21	254	148	21	239	109
22	254	147	22	136	107
23	254	146	23	245	108
24	252	145	24	254	109
25	254	145	25	245	111
26	248	147	26	248	110
27	251	132	27	249	110
28	177	144	28	254	111
29	254	147	29	247	113
30	247	148	30	243	109
31	250	145	31	250	114
32	250	133	32	245	110
33	254	144	33	254	109
34	251	143	34	254	111
35	254	142	35	254	111
36	254	141	36	180	114
37	247	140	37	254	110
38	164	136	38	246	112
39	250	128	39	252	112
40	252	127	40	247	111
41	250	127	41	244	116

SPP (oval-clear) MAX Data			PET (round-white) MAX Data		
Cycle #	MAX Energy (Joules)	MAX Power (Watts)	Cycle #	MAX Energy (Joules)	MAX Power (Watts)
42	249	136	42	243	114
43	254	121	43	253	113
44	254	133	44	247	115
45	253	122	45	227	113
46	249	115	46	247	120
47	249	102	47	244	117
48	251	94	48	250	115
49	253	129	49	182	117
50	254	102	50	254	118
51	244	104	51	248	121
52	254	100	52	162	118
53	253	120	53	254	120
54	247	122	54	250	125
55	254	115	55	245	119
56	247	118	56	245	116
57	254	128	57	242	123
58	254	128	58	252	116
59	253	99	59	246	121
60	250	127	60	254	129
61	252	128	61	244	124
62	250	101	62	248	124
63	254	125	63	202	118
64	254	100	64	254	120
65	242	100	65	243	120
66	254	123	66	254	117
67	167	94	67	246	131
68	250	98	68	242	126
69	249	99	69	204	125
70	252	100	70	251	121
71	254	100	71	251	125
72	248	95	72	243	126
73	182	124	73	244	125
74	250	124	74	250	124
75	238	97	75	245	127
76	249	123	76	248	123
77	249	123	77	250	121
78	247	120	78	248	122
79	254	121	79	251	132
80	254	117	80	254	134
81	117	115	81	251	131
82	254	115	82	245	128
83	243	100	83	252	128

SPP (oval-clear) MAX Data			PET (round-white) MAX Data		
Cycle #	MAX Energy (Joules)	MAX Power (Watts)	Cycle #	MAX Energy (Joules)	MAX Power (Watts)
84	242	118	84	172	172
85	254	116	85	165	165
86	250	97	86	251	129
87	254	98	87	160	137
88	248	115	88	207	132
89	220	95	89	243	128
90	252	102	90	248	141
91	254	98	91	254	133
92	246	97	92	248	130
93	250	98	93	254	134
94	246	97	94	254	138
95	243	102	95	230	126
96	248	102	96	254	136
97	233	98	97	242	128
98	242	98	98	253	136
99	254	113	99	254	134
100	247	100	100	245	131
101	254	97	101	249	137
102	220	116	102	246	134
103	250	113	103	229	147
104	252	102	104	172	130
105	250	114	105	254	141
106	254	101	106	245	136
107	249	101	107	252	136
108	254	115	108	250	139
109	242	97	109	240	137
110	245	101	110	252	136
111	244	97	111	249	136
112	248	92	112	241	143
113	242	98	113	250	135
114	197	96	114	245	133
115	252	115	115	227	130
116	250	114	116	162	129
117	223	112	117	239	132
118	151	114	118	185	125
119	246	101	119	252	132
120	236	101	120	254	143
121	241	101	121	168	134
122	245	101	122	204	140
123	253	94	123	252	141
124	254	110	124	243	135
125	248	101	125	245	147

SPP (oval-clear) MAX Data			PET (round-white) MAX Data		
Cycle #	MAX Energy (Joules)	MAX Power (Watts)	Cycle #	MAX Energy (Joules)	MAX Power (Watts)
126	160	95	126	239	132
127	245	110	127	246	136
128	254	99	128	249	134
129	254	98	129	245	140
130	247	95	130	250	150
131	243	92	131	253	138
132	245	111	132	250	133
133	254	98	133	247	125
134	241	126	134	250	137
135	251	116	135	254	123
136	254	124	136	182	134
137	249	120	137	250	127
138	188	131	138	245	132
139	251	133	139	249	120
140	254	103	140	211	137
141	199	132	141	232	133
142	252	131	142	254	129
143	254	129	143	239	125
144	246	130	144	251	131
145	213	131	145	242	128
146	228	129	146	254	133
147	254	128	147	196	140
148	254	128	148	243	134
149	252	126	149	240	136
150	129	125	150	134	134
151	252	121	151	254	137
152	191	123	152	246	140
153	142	101	153	252	138
154	241	96	154	251	126
155	254	100	155	242	120
156	238	100	156	252	129
157	252	92	157	252	136
158	254	99	158	250	136
159	252	121	159	242	125
160	249	98	160	251	128
161	254	120	161	254	151
162	254	119	162	247	130
163	243	99	163	243	146
164	250	119	164	252	134
165	254	119	165	252	132
166	249	114	166	251	130
167	249	108	167	204	130

SPP (oval-clear) MAX Data			PET (round-white) MAX Data		
Cycle #	MAX Energy (Joules)	MAX Power (Watts)	Cycle #	MAX Energy (Joules)	MAX Power (Watts)
168	254	94	168	254	145
169	244	115	169	247	128
170	235	114	170	244	130
			171	251	135
			172	240	121
			173	245	130
			174	252	123
			175	244	126
			176	254	132
			177	252	135
			178	129	129
			179	248	131
			180	251	133
			181	222	132
			182	237	148
			183	249	145
			184	241	133
			185	245	221
			186	244	229
			187	247	178
			188	252	132
			189	246	136
			190	240	131
			191	234	128
			192	192	127
			193	148	129
			194	241	132
			195	221	118
			196	254	143
			197	241	136
			198	153	125
			199	244	142
			200	252	150
			201	249	138
			202	242	140
			203	244	143
			204	250	149
			205	206	144
			206	165	136
			207	245	148
			208	250	143

HDPE (round-white) MAX Data		
Cycle #	MAX Energy (Joules)	MAX Power (Watts)
1	239	84
2	254	85
3	241	87
4	252	87
5	254	88
6	254	87
7	252	87
8	254	87
9	240	87
10	247	86
11	243	87
12	250	87
13	254	86
14	254	85
15	254	85
16	246	85
17	254	84
18	254	84
19	243	84
20	238	84
21	253	84
22	254	84
23	250	84
24	238	85
25	245	85
26	249	83
27	254	84
28	253	84
29	244	84
30	254	84
31	238	84
32	246	84
33	240	84
34	254	83
35	239	84
36	247	83
37	251	84
38	247	84
39	253	83
40	238	84

HDPE (round-white) MAX Data		
Cycle #	MAX Energy (Joules)	MAX Power (Watts)
41	241	84
42	241	83
43	244	84
44	254	85
45	246	85
46	254	84
47	239	83
48	239	84
49	254	84
50	179	83
51	246	84
52	138	85
53	244	84
54	248	84
55	248	85
56	165	84
57	252	84
58	250	84
59	244	84
60	240	84
61	241	85
62	159	83
63	254	84
64	241	84
65	167	84
66	241	84
67	246	83
68	162	84
69	254	84
70	246	84
71	247	84
72	142	83
73	243	84
74	132	84
75	239	84
76	185	84
77	250	83
78	198	84
79	245	84
80	244	83
81	238	84
82	245	84

HDPE (round-white) MAX Data		
Cycle #	MAX Energy (Joules)	MAX Power (Watts)
83	249	84
84	199	84
85	247	84
86	246	84
87	251	84
88	248	84
89	249	84
90	246	83
91	249	84
92	249	84
93	245	84
94	254	84
95	243	84
96	179	84
97	240	84
98	241	84
99	176	84
100	251	85
101	246	84
102	202	84
103	188	84
104	243	84
105	243	84
106	250	84
107	250	84
108	251	84
109	242	84
110	220	84
111	249	84
112	244	84
113	254	85
114	137	84
115	237	84
116	252	85
117	252	85
118	254	84
119	242	84
120	204	85
121	218	84
122	246	83
123	254	84
124	252	84

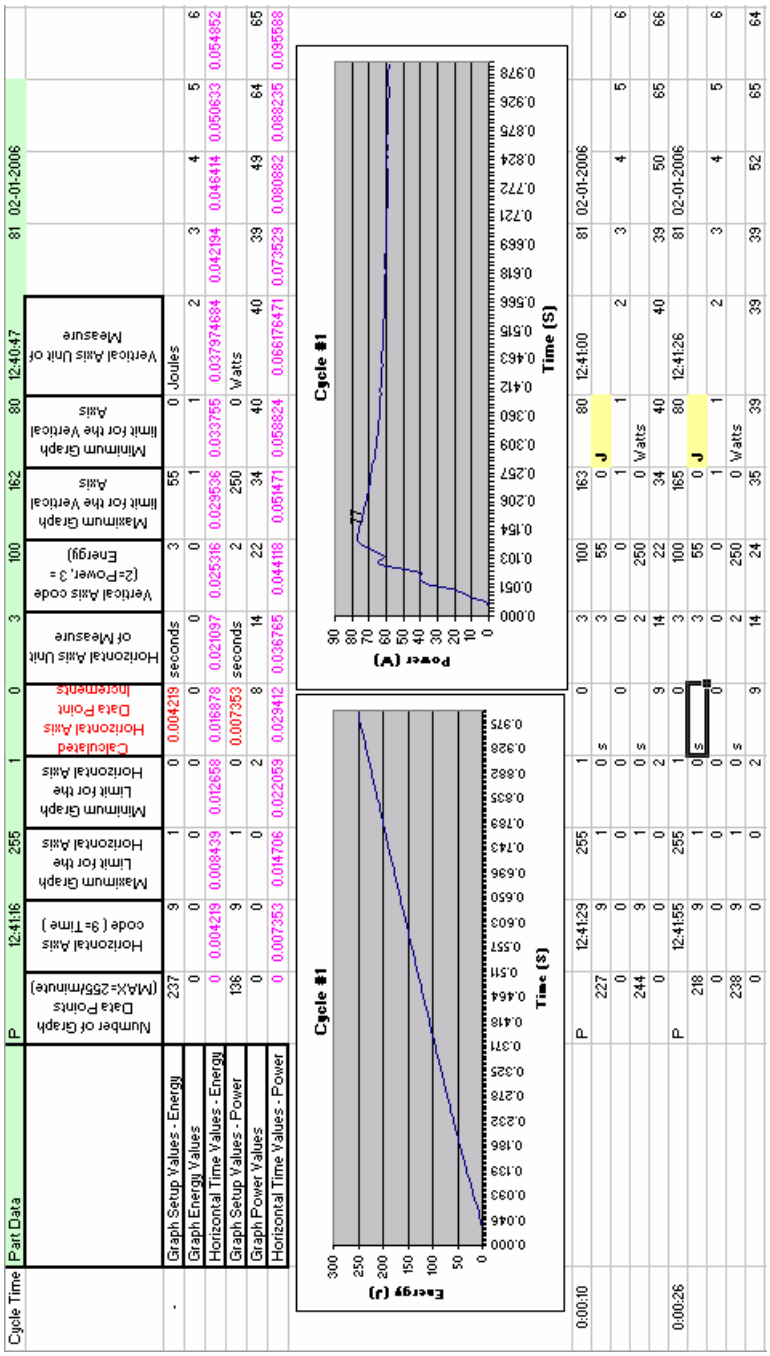
HDPE (round-white) MAX Data		
Cycle #	MAX Energy (Joules)	MAX Power (Watts)
125	219	84
126	247	84
127	242	84
128	237	84
129	243	84
130	225	84
131	188	84
132	238	83
133	244	84
134	254	83
135	242	84
136	253	83
137	247	83
138	208	83
139	242	83
140	251	83
141	150	83
142	252	84
143	240	84
144	247	84
145	247	84
146	217	84
147	254	83
148	249	85
149	236	84
150	241	83
151	238	83
152	217	84
153	243	85
154	233	83
155	253	84
156	240	84
157	245	83
158	241	85
159	251	84
160	244	84
161	192	84
162	247	83
163	252	84
164	250	83
165	252	83
166	206	84

HDPE (round-white) MAX Data		
Cycle #	MAX Energy (Joules)	MAX Power (Watts)
167	233	83
168	238	83
169	240	84
170	246	83
171	246	83
172	254	83
173	243	83
174	243	83
175	251	84
176	252	84
177	254	83
178	240	83
179	254	83
180	242	84
181	250	83
182	173	83
183	245	83
184	244	83
185	242	83
186	207	83
187	244	84
188	252	84
189	245	84
190	247	84
191	206	84
192	205	84
193	254	84
194	245	84

D.2. Collected Raw Data

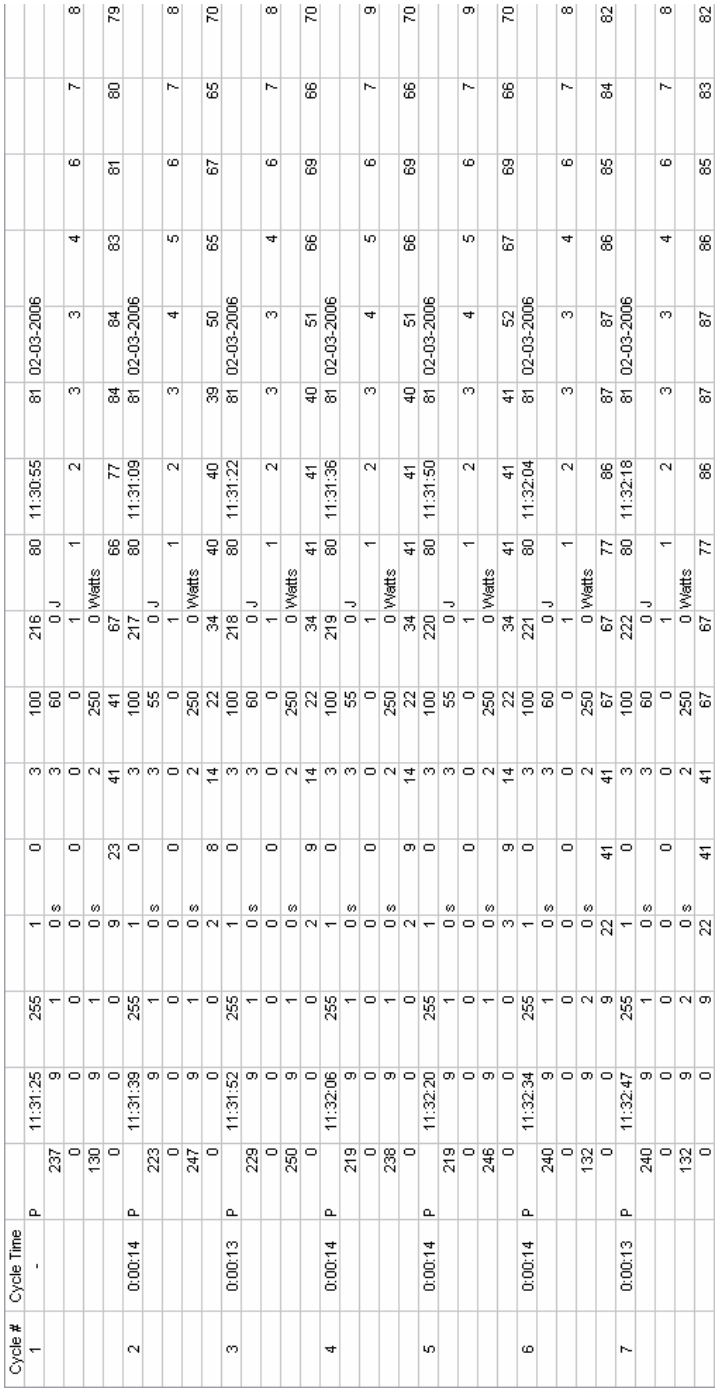
D.2.1 – 20060201 LDPE 8ml Round.xls

(representative data for 3 cycles, # of cycles = 147, columns of data vary to 255)



D.2.2 – 20060203 HDPE 4oz Round.xls

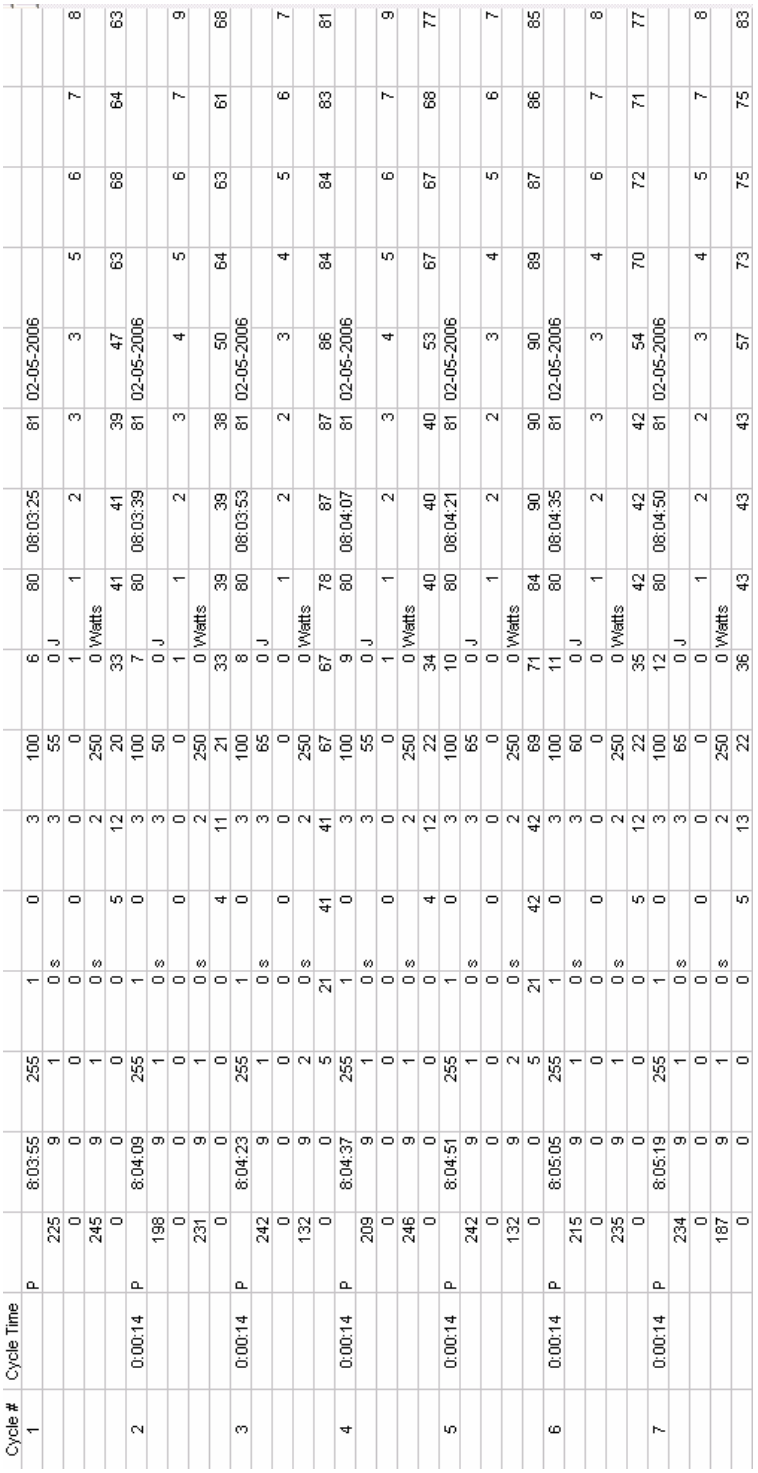
(representative data for 7 cycles, # of cycles = 194, columns of data vary to 255)



| Cycle # | Cycle Time | | |

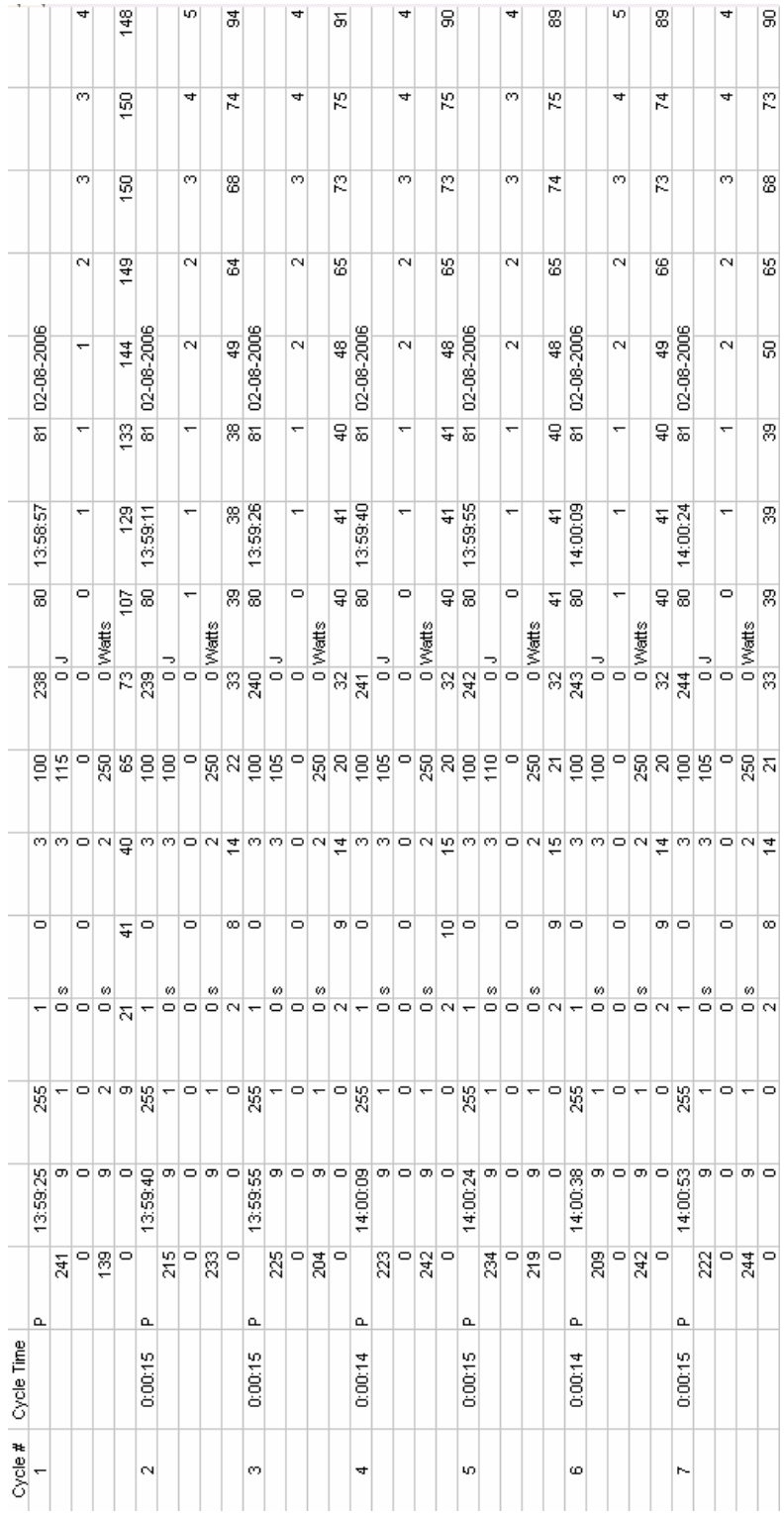
D.2.3 – 20060205 PET 2oz PET Round.xls

(representative data for 7 cycles, # of cycles = 208, columns of data vary to 255)



| Cycle # | Cycle Time | | |

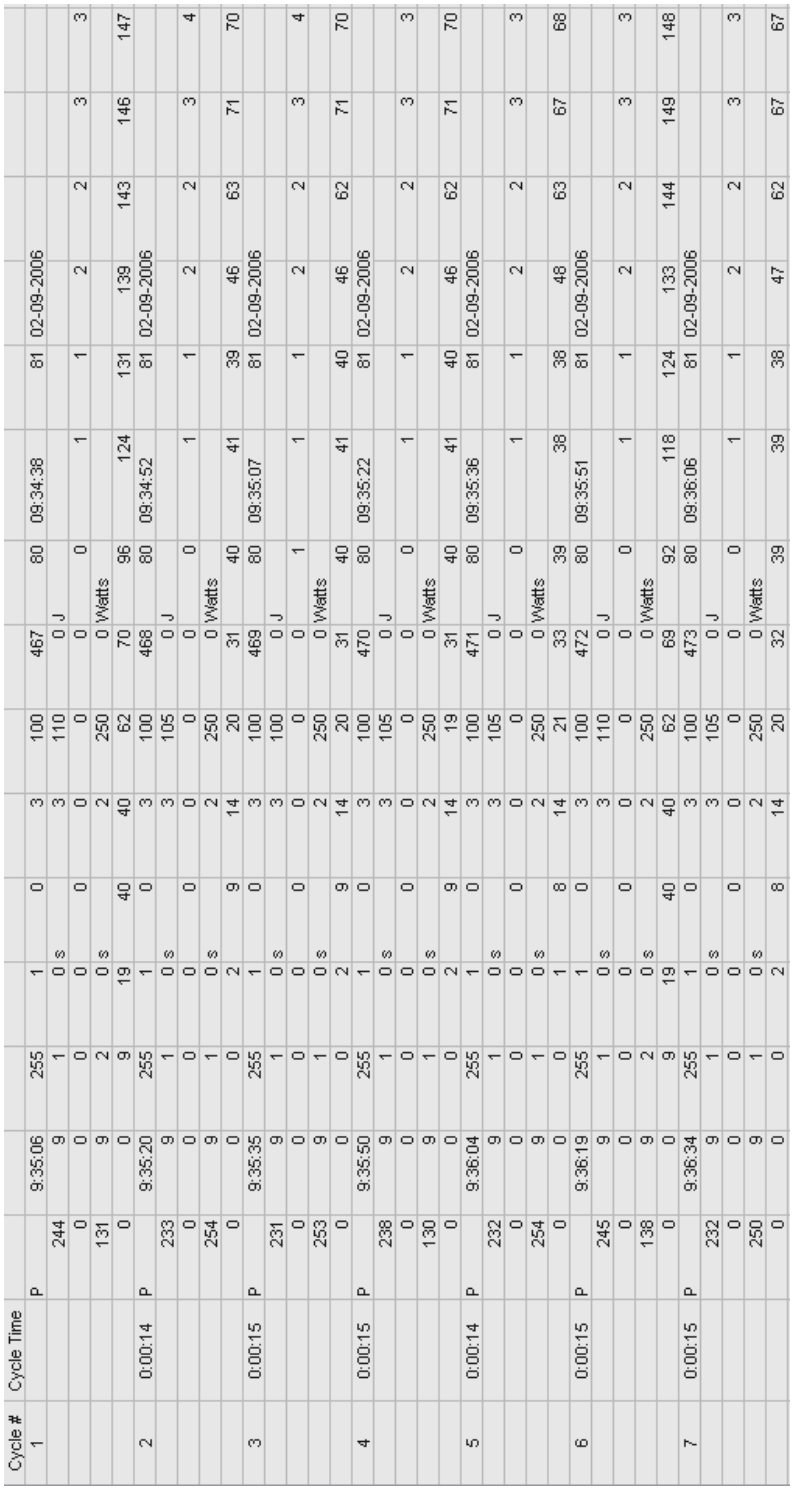
(representative data for 7 cycles, # of cycles = 201, columns of data vary to 255)



| Cycle # | Cycle Time | | |

D.2.5 – 20060209 SPP 7_5ml Oval Clear.xls

(representative data for 7 cycles, # of cycles = 170, columns of data vary to 255)



| Cycle # | Cycle Time | | |

D.2.6 – Test Phase 10, Non-Viable Particle Count Data

Time Stamp	PPS, 0.05	PPS, 5.0	Room, 0.05	Room, 5.0	Corridor, 0.05	Corridor, 5.0
8:17	47	0	12	0	9	0
8:18	44	0	9	0	9	0
8:19	63	0	7	0	9	0
8:20	76	0	6	0	9	0
8:21	85	0	5	0	18	1
8:22	83	0	13	0	69	13
8:23	113	0	12	0	68	14
8:24	648	7	11	0	68	14
8:25	598	6	16	0	68	14
8:26	548	6	15	0	68	14
8:27	509	5	13	0	68	14
8:28	480	5	13	0	69	14
8:29	450	5	12	0	70	14
8:30	422	4	11	0	69	14
8:31	412	4	12	0	69	14
8:32	410	4	12	0	69	14
8:33	392	4	11	0	69	14
8:34	373	4	11	0	69	14
8:35	362	3	10	0	71	15
8:36	347	3	13	0	73	15
8:37	338	3	12	0	75	15
8:38	325	3	13	0	75	15
8:39	318	3	14	0	76	15
8:40	307	3	15	0	76	15
8:41	306	3	18	0	101	15
8:42	300	3	18	0	101	15
8:43	290	2	17	0	107	15
8:44	281	2	16	0	107	15
8:45	273	2	16	0	114	15
8:46	267	2	16	0	122	15
8:47	259	2	16	0	130	15
8:48	307	2	18	0	138	15
8:49	299	2	17	0	146	15
8:50	298	2	17	0	150	15
8:51	299	2	16	0	157	15
8:52	301	2	16	0	163	15
8:53	300	2	16	0	168	15
8:54	297	2	16	0	168	15
8:55	293	2	16	0	175	15

Time Stamp	PPS, 0.05	PPS, 5.0	Room, 0.05	Room, 5.0	Corridor, 0.05	Corridor, 5.0
8:56	290	2	16	0	170	14
8:57	292	2	15	0	117	2
8:58	283	2	16	0	118	1
8:59	127	0	16	0	121	1
9:00	126	0	14	0	125	1
9:01	126	0	14	0	130	1
9:02	137	0	16	0	133	1
9:03	143	0	17	0	133	1
9:04	148	0	18	0	132	1
9:05	150	0	18	0	133	1
9:06	150	0	17	0	135	1
9:07	141	0	17	0	136	1
9:08	141	0	17	0	136	1
9:09	147	0	18	0	136	1
9:10	151	0	18	0	135	0
9:11	154	0	17	0	138	0
9:12	157	0	17	0	136	0
9:13	162	0	16	0	136	0
9:14	165	0	16	0	138	0
9:15	166	0	15	0	138	0
9:16	159	0	12	0	114	0
9:17	161	0	12	0	114	0
9:18	163	0	12	0	110	0
9:19	164	0	12	0	110	0
9:20	164	0	12	0	103	0
9:21	163	0	11	0	95	0
9:22	166	0	11	0	88	0
9:23	166	0	11	0	88	0
9:24	161	0	10	0	72	0
9:25	169	0	11	0	68	0
9:26	170	0	11	0	62	0
9:27	178	0	11	0	57	0
9:28	186	0	11	0	52	0
9:29	193	0	11	0	53	0
9:30	204	0	11	0	47	0
9:31	242	0	11	0	43	0
9:32	242	0	11	0	43	0
9:33	241	0	10	0	40	0
9:34	243	0	11	0	38	0
9:35	248	0	11	0	33	0
9:36	255	0	11	0	34	0

Time Stamp	PPS, 0.05	PPS, 5.0	Room, 0.05	Room, 5.0	Corridor, 0.05	Corridor, 5.0
9:37	245	0	10	0	33	0
9:38	237	0	12	0	37	0
9:39	234	0	12	0	38	0
9:40	233	0	12	0	37	0
9:41	226	0	12	0	47	0
9:42	262	0	12	0	51	0
9:43	262	0	12	0	98	0
9:44	258	0	12	0	135	1
9:45	264	0	13	0	164	2
9:46	268	0	12	0	159	2
9:47	299	0	12	0	159	2
9:48	303	0	12	0	160	2
9:49	302	0	12	0	158	2
9:50	302	0	13	0	158	2
9:51	320	0	13	0	158	2
9:52	336	0	13	0	158	2
9:53	338	0	14	0	156	2
9:54	341	0	14	0	156	2
9:55	344	0	14	0	156	2
9:56	346	0	15	0	157	2
9:57	360	0	15	0	156	2
9:58	384	0	16	0	157	2
9:59	377	0	16	0	157	2
10:00	392	0	16	0	158	2
10:01	400	0	16	0	178	2
10:02	390	0	16	0	182	2
10:03	414	0	16	0	183	2
10:04	409	0	16	0	182	2
10:05	411	0	17	0	191	3
10:06	376	0	18	0	193	3
10:07	387	0	18	0	193	3
10:08	413	0	18	0	194	3
10:09	445	0	17	0	194	3
10:10	452	0	18	0	195	3
10:11	463	0	18	0	189	3
10:12	466	0	18	0	188	3
10:13	474	0	15	0	184	3
10:14	480	0	14	0	184	3
10:15	494	0	14	0	185	3
10:16	540	0	15	0	174	3
10:17	505	0	15	0	169	3

Time Stamp	PPS, 0.05	PPS, 5.0	Room, 0.05	Room, 5.0	Corridor, 0.05	Corridor, 5.0
10:18	510	0	16	0	123	3
10:19	520	0	16	0	86	2
10:20	511	0	16	0	56	1
10:21	510	0	17	0	56	1
10:22	485	0	17	0	56	1
10:23	480	0	18	0	55	1
10:24	483	0	18	0	56	1
10:25	487	0	17	0	56	1
10:26	479	0	17	0	55	1
10:27	461	0	17	0	55	1
10:28	460	0	16	0	55	1
10:29	463	0	16	0	54	1
10:30	461	0	16	0	54	1
10:31	461	0	16	0	54	1
10:32	459	0	16	0	54	1
10:33	463	0	15	0	53	1
10:34	434	0	15	0	54	1
10:35	413	0	14	0	53	1
10:36	404	0	14	0	32	1
10:37	408	0	15	0	27	1
10:38	418	0	15	0	26	1
10:39	418	0	16	0	26	1
10:40	406	0	16	0	16	0
10:41	406	0	15	0	16	0
10:42	396	0	14	0	16	0
10:43	382	0	14	0	15	0
10:44	356	0	14	0	14	0
10:45	360	0	13	0	13	0
10:46	360	0	13	0	13	0
10:47	377	0	12	0	13	0
10:48	388	0	12	0	12	0
10:49	386	0	12	0	11	0
10:50	374	0	12	0	10	0
10:51	337	0	13	0	9	0
10:52	351	0	13	0	11	1
10:53	346	0	13	0	11	1
10:54	354	0	12	0	10	1
10:55	377	0	11	0	10	1
10:56	370	0	10	0	10	1
10:57	398	0	10	0	11	1
10:58	419	0	9	0	11	1

Time Stamp	PPS, 0.05	PPS, 5.0	Room, 0.05	Room, 5.0	Corridor, 0.05	Corridor, 5.0
10:59	412	0	8	0	9	1
11:00	407	0	8	0	10	1
11:01	399	0	10	0	10	1
11:02	406	0	11	0	10	1
11:03	418	0	11	0	13	1
11:04	420	0	11	0	13	1
11:05	464	0	11	0	14	1
11:06	472	0	11	0	13	1
11:07	460	0	12	0	13	1
11:08	430	0	12	0	13	1
11:09	424	0	12	0	14	1
11:10	422	0	12	0	14	1
11:11	421	0	12	0	14	1
11:12	418	0	11	0	14	1
11:13	380	0	11	0	14	1
11:14	380	0	10	0	14	1
11:15	380	0	10	0	15	1
11:16	378	0	10	0	13	1
11:17	375	0	10	0	14	1
11:18	363	0	11	0	15	1
11:19	359	0	11	0	15	1
11:20	341	0	12	0	15	1
11:21	324	0	12	0	15	1
11:22	304	0	12	0	14	1
11:23	285	0	12	0	14	1
11:24	285	0	13	0	14	1
11:25	284	0	13	0	14	1
11:26	276	0	11	0	14	1
11:27	268	0	11	0	13	0
11:28	271	0	10	0	12	0
11:29	255	0	10	0	12	0
11:30	227	0	10	0	13	0
11:31	229	0	10	0	15	0
11:32	189	0	11	0	14	0
11:33	178	0	12	0	14	0
11:34	181	0	12	0	14	0
11:35	187	0	13	0	14	0
11:36	185	0	11	0	14	0
11:37	176	0	10	0	16	0
11:38	164	0	10	0	13	0
11:39	160	0	11	0	13	0

Time Stamp	PPS, 0.05	PPS, 5.0	Room, 0.05	Room, 5.0	Corridor, 0.05	Corridor, 5.0
11:40	115	0	11	0	12	0
11:41	112	0	10	0	13	0
11:42	114	0	9	0	14	0
11:43	117	0	10	0	16	0
11:44	114	0	9	0	14	0
11:45	113	0	10	0	14	0
11:46	113	0	10	0	15	0
11:47	111	0	10	0	16	0
11:48	112	0	10	0	17	0
11:49	112	0	10	0	17	0
11:50	116	0	9	0	17	0
11:51	114	0	9	0	17	0
11:52	114	0	9	0	16	0
11:53	117	0	8	0	16	0
11:54	141	0	8	0	16	0
11:55	232	0	7	0	16	0
11:56	326	0	8	0	16	0
11:57	328	0	8	0	16	0
11:58	328	0	8	0	16	0
11:59	321	0	7	0	16	0
12:00	322	0	8	0	16	0
12:01	321	0	9	0	16	0
12:02	314	0	9	0	15	0
12:03	313	0	9	0	15	0
12:04	312	0	9	0	15	0
12:05	317	0	9	0	14	0
12:06	319	0	11	0	12	0
12:07	326	0	11	0	12	0
12:08	318	0	10	0	12	0
12:09	315	0	10	0	12	0
12:10	318	0	10	0	11	0
12:11	322	0	10	0	11	0
12:12	320	0	10	0	9	0
12:13	321	0	10	0	9	0
12:14	318	0	11	0	9	0
12:15	319	0	12	0	9	0
12:16	316	0	13	0	8	0
12:17	311	0	13	0	7	0
12:18	307	0	13	0	6	0
12:19	306	0	14	0	6	0
12:20	310	0	13	0	7	0

Time Stamp	PPS, 0.05	PPS, 5.0	Room, 0.05	Room, 5.0	Corridor, 0.05	Corridor, 5.0
12:21	313	0	15	0	6	0
12:22	315	0	15	0	5	0
12:23	313	0	16	0	4	0
12:24	312	0	16	0	4	0
12:25	312	0	16	0	4	0
12:26	316	0	16	0	4	0
12:27	315	0	16	0	5	0
12:28	316	0	16	0	6	0
12:29	294	0	17	0	7	0
12:30	204	0	18	0	8	0
12:31	115	0	17	0	8	0
12:32	112	0	17	0	8	0
12:33	111	0	17	0	8	0
12:34	119	0	17	0	8	0
12:35	119	0	17	0	8	0
12:36	127	0	17	0	8	0
12:37	125	0	18	0	9	0
12:38	125	0	18	0	9	0
12:39	130	0	19	0	9	0
12:40	133	0	20	0	9	0
12:41	132	0	18	0	10	0
12:42	127	0	18	0	10	0
12:43	122	0	18	0	10	0
12:44	125	0	19	0	10	0
12:45	118	0	19	0	10	0
12:46	118	0	19	0	11	0
12:47	123	0	19	0	11	0
12:48	123	0	21	0	11	0
12:49	124	0	20	0	11	0
12:50	128	0	19	0	11	0
12:51	126	0	18	0	11	0
12:52	130	0	18	0	11	0
12:53	135	0	17	0	10	0
12:54	138	0	17	0	10	0
12:55	140	0	18	0	10	0
12:56	137	0	16	0	12	0
12:57	137	0	16	0	12	0
12:58	140	0	15	0	12	0
12:59	142	0	16	0	12	0
13:00	137	0	16	0	11	0
13:01	136	0	16	0	11	0

Time Stamp	PPS, 0.05	PPS, 5.0	Room, 0.05	Room, 5.0	Corridor, 0.05	Corridor, 5.0
13:02	140	0	16	0	10	0
13:03	147	0	18	0	8	0
13:04	151	0	17	0	10	0
13:05	150	0	17	0	9	0
13:06	144	0	18	0	9	0
13:07	144	0	18	0	9	0
13:08	144	0	19	0	9	0
13:09	140	0	19	0	9	0
13:10	140	0	18	0	10	0
13:11	136	0	18	0	10	0
13:12	148	0	18	0	11	0
13:13	150	0	20	0	11	0
13:14	147	0	20	0	12	0
13:15	158	0	20	0	12	0
13:16	166	0	20	0	11	0
13:17	176	0	20	0	12	0
13:18	177	0	21	0	12	0
13:19	177	0	20	0	14	0
13:20	177	0	19	0	15	0
13:21	187	0	19	0	15	0
13:22	183	0	19	0	17	0
13:23	183	0	19	0	17	0
13:24	205	0	17	0	17	0
13:25	227	0	17	0	19	0
13:26	225	0	17	0	20	0
13:27	229	0	18	0	20	0
13:28	230	0	19	0	21	0
13:29	228	0	19	0	22	0
13:30	257	0	19	0	21	0
13:31	264	0	20	0	19	0
13:32	291	0	21	0	21	0
13:33	287	0	21	0	22	0
13:34	299	0	21	0	23	0
13:35	301	0	21	0	24	0
13:36	301	0	21	0	24	0
13:37	315	0	21	0	25	0
13:38	304	0	19	0	25	0
13:39	302	0	19	0	23	0
13:40	303	0	18	0	23	0
13:41	311	0	17	0	24	0
13:42	310	0	17	0	25	0

Time Stamp	PPS, 0.05	PPS, 5.0	Room, 0.05	Room, 5.0	Corridor, 0.05	Corridor, 5.0
13:43	314	0	18	0	26	0
13:44	338	0	18	0	28	0
13:45	337	0	18	0	29	0
13:46	338	0	18	0	29	0
13:47	336	0	17	0	27	0
13:48	334	0	15	0	27	0
13:49	329	0	15	0	27	0
13:50	313	0	14	0	31	1
13:51	307	0	14	0	36	1
13:52	297	0	13	0	37	1
13:53	299	0	13	0	39	1
13:54	298	0	13	0	42	1
13:55	295	0	13	0	42	1
13:56	285	0	13	0	42	1
13:57	285	0	13	0	42	1
13:58	283	0	13	0	57	1
13:59	265	0	12	0	59	1
14:00	241	0	12	0	59	1
14:01	254	0	12	0	58	1
14:02	255	0	11	0	59	1
14:03	256	0	10	0	71	1
14:04	257	0	9	0	70	1
14:05	225	0	9	0	71	2
14:06	218	0	8	0	86	2
14:07	189	0	8	0	87	2
14:08	194	0	8	0	87	2
14:09	183	0	8	0	86	2
14:10	186	0	8	0	86	2
14:11	177	0	8	0	88	2
14:12	165	0	8	0	87	2
14:13	166	0	8	0	89	2
14:14	159	0	8	0	90	2
14:15	167	0	10	0	104	4
14:16	172	0	10	0	104	4
14:17	174	0	11	0	104	4
14:18	177	0	9	0	104	4
14:19	193	0	9	0	104	4
14:20	191	0	10	0	102	4
14:21	191	0	9	0	102	4
14:22	190	0	9	0	103	4
14:23	201	0	9	0	104	4

Time Stamp	PPS, 0.05	PPS, 5.0	Room, 0.05	Room, 5.0	Corridor, 0.05	Corridor, 5.0
14:24	230	0	10	0	103	4
14:25	233	0	10	0	99	3
14:26	233	0	11	0	94	3
14:27	239	0	11	0	93	3
14:28	237	0	11	0	91	3
14:29	248	0	12	0	87	3
14:30	254	0	12	0	86	3
14:31	255	0	12	0	86	3
14:32	256	0	12	0	85	3
14:33	256	0	12	0	71	3
14:34	256	0	12	0	70	3
14:35	254	0	12	0	80	3
14:36	246	0	12	0	83	3
14:37	240	0	13	0	85	3
14:38	237	0	13	0	72	3
14:39	282	0	13	0	73	3
14:40	285	0	12	0	72	2
14:41	290	0	12	0	58	2
14:42	297	0	11	0	55	2
14:43	295	0	11	0	56	2
14:44	296	0	10	0	58	2
14:45	351	0	11	0	60	2
14:46	439	0	11	0	58	2
14:47	459	0	11	0	59	2
14:48	469	0	11	0	57	2
14:49	493	0	12	0	55	2
14:50	486	0	10	0	43	0
14:51	475	0	10	0	44	0
14:52	485	0	9	0	44	0
14:53	492	0	10	0	45	0
14:54	449	0	10	0	44	0
14:55	451	0	9	0	44	0
14:56	450	0	9	0	44	0
14:57	442	0	9	0	47	0
14:58	429	0	9	0	48	0
14:59	405	0	7	0	50	0
15:00	404	0	8	0	50	0
15:01	400	0	7	0	50	0
15:02	395	0	7	0	49	0
15:03	396	0	6	0	51	0
15:04	382	0	5	0	50	0

Time Stamp	PPS, 0.05	PPS, 5.0	Room, 0.05	Room, 5.0	Corridor, 0.05	Corridor, 5.0
15:05	377	0	6	0	50	0
15:06	384	0	6	0	50	0
15:07	399	0	7	0	51	0
15:08	395	0	7	0	50	0
15:09	393	0	7	0	49	0
15:10	398	0	7	0	38	0
15:11	399	0	7	0	35	0
15:12	402	0	6	0	35	0
15:13	416	0	7	0	37	0
15:14	370	0	7	0	37	0
15:15	367	0	7	0	38	0
15:16	367	0	7	0	37	0
15:17	390	0	8	0	37	0
15:18	411	0	8	0	35	0
15:19	429	0	10	0	33	0
15:20	390	0	9	0	31	0
15:21	376	0	9	0	31	0
15:22	363	0	9	0	30	0
15:23	371	0	10	0	30	0
15:24	351	0	9	0	30	0
15:25	351	0	9	0	29	0
15:26	357	0	11	0	27	0
15:27	359	0	12	0	26	0
15:28	346	0	11	0	24	0
15:29	382	0	12	0	24	0
15:30	394	0	12	0	24	0
15:31	398	0	13	0	25	0
15:32	401	0	14	0	22	0
15:33	403	0	14	0	21	0
15:34	405	1	14	0	19	0
15:35	403	1	13	0	19	0
15:36	417	1	13	0	21	0
15:37	418	1	13	0	21	0
15:38	418	1	13	0	19	0
15:39	425	1	13	0	19	0
15:40	426	1	12	0	19	0
15:41	415	1	12	0	18	0
15:42	399	1	12	0	16	0
15:43	400	1	12	0	16	0
15:44	407	1	12	0	51	4
15:45	410	1	12	0	162	9

Time Stamp	PPS, 0.05	PPS, 5.0	Room, 0.05	Room, 5.0	Corridor, 0.05	Corridor, 5.0
15:46	407	1	12	0	166	9
15:47	404	1	12	0	164	9
15:48	386	1	11	0	164	9
15:49	403	1	13	0	163	9
15:50	404	1	14	0	163	9
15:51	403	1	14	0	164	9
15:52	378	1	13	0	164	9
15:53	355	1	13	0	164	9
15:54	336	1	11	0	164	9
15:55	323	1	12	0	164	9
15:56	256	1	12	0	167	9
15:57	256	1	13	0	167	9
15:58	244	1	12	0	168	9
15:59	242	1	13	0	168	9
16:00	242	1	13	0	168	9
16:01	237	1	11	0	168	9
16:02	226	1	10	0	168	9
16:03	240	1	11	0	169	9
16:04	217	1	10	0	168	9
16:05	211	1	12	0	169	9
16:06	211	1	11	0	169	9
16:07	232	1	10	0	171	9
16:08	228	1	10	0	171	9
16:09	233	0	10	0	172	9
16:10	231	0	11	0	173	9
16:11	219	0	12	0	173	9
16:12	218	0	12	0	174	9
16:13	215	0	12	0	175	9
16:14	217	0	12	0	177	9
16:15	225	0	12	0	177	9
16:16	239	0	12	0	177	9
16:17	242	0	11	0	178	9
16:18	262	0	11	0	178	9
16:19	265	0	11	0	144	5
16:20	259	0	11	0	32	0
16:21	260	0	13	0	28	0
16:22	261	0	15	0	27	0
16:23	282	0	15	0	25	0
16:24	283	0	13	0	25	0
16:25	284	0	12	0	25	1
16:26	282	0	12	0	24	1

Time Stamp	PPS, 0.05	PPS, 5.0	Room, 0.05	Room, 5.0	Corridor, 0.05	Corridor, 5.0
16:27	278	0	13	0	24	1
16:28	277	0	13	0	24	1
16:29	283	0	13	0	25	1
16:30	277	0	12	0	24	1
16:31	273	0	12	0	22	1
16:32	269	0	11	0	22	1
16:33	276	0	11	0	21	1
16:34	275	0	10	0	25	1
16:35	274	0	10	0	24	1
16:36	285	0	10	0	24	1
16:37	297	0	10	0	25	1
16:38	282	0	9	0	24	1
16:39	303	0	10	0	24	1
16:40	378	0	8	0	25	1
16:41	371	0	8	0	24	1
16:42	346	0	8	0	23	1
16:43	346	0	8	0	22	1
16:44	346	0	8	0	22	1
16:45	335	0	8	0	20	1
16:46	332	0	7	0	18	1
16:47	328	0	7	0	17	1
16:48	328	0	7	0	16	1

APPENDIX E

SOFTWARE FOR RAW DATA COLLECTION

Dukane's iPC software was utilized via a serial cable connection provided on the ultrasonic generator and one on a notebook/host PC running Windows XP. The iPC application software runs within XP and requires the use of a feature within Microsoft's Internet Explorer program which is called the Java Virtual Machine (JVM). Although the JVM from Microsoft was based on the JVM from Sun Microsystems, iPC is not compatible with the JVM from Sun Microsystems. If the Sun Microsystems JVM has been installed on the host PC for the iPC program, you must disable the Sun Microsystems JVM before using iPC. iPC will scan your PC each time the iPC program is activated to confirm that the Sun Microsystems JVM is not active.

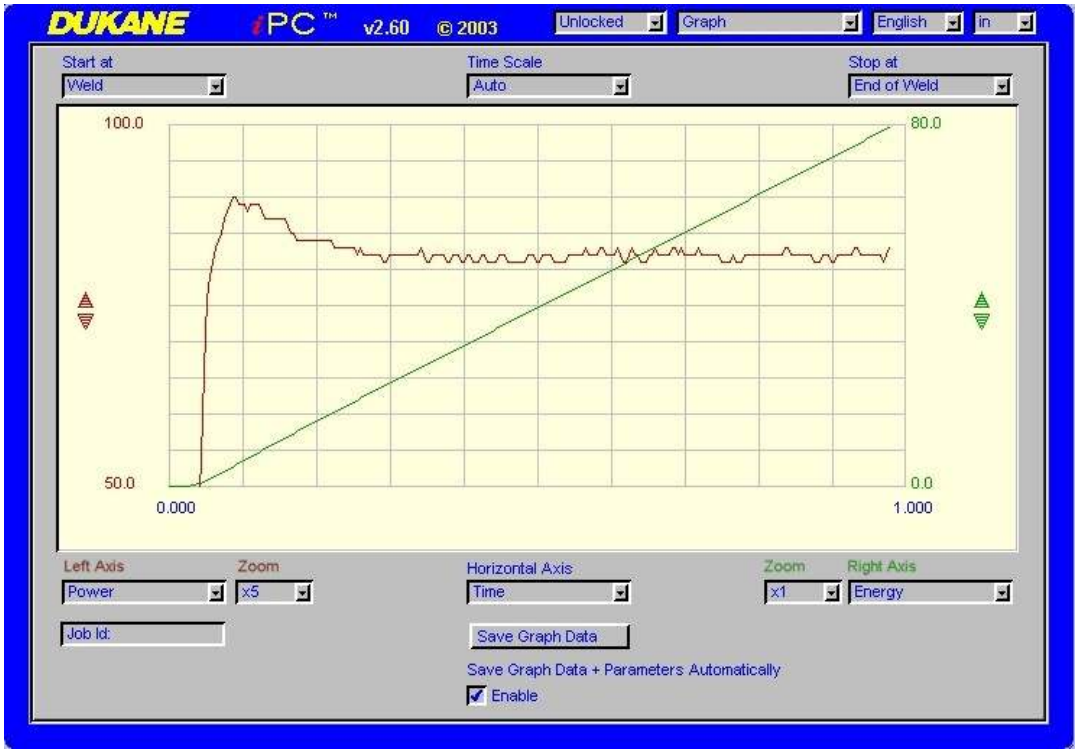
A checkbox on the page "Graph":

- Title: "Save Graph Data + Parameters Automatically"
- Activation: "Enabled" if checked (default is "Disabled", or unchecked)

This feature allows the user to save part data and graph data for each weld cycle automatically to the host PC hard drive.

After allowing iPC to connect to the ultrasonic generator, navigate to the "Graph" page of the iPC software. Enable the "Save Graph Data + Parameters

Automatically" box at the bottom of the graph page by placing a check mark in the "Enable" box.



When saving graph data and parameters is enabled, iPC creates, for every new part, a set of lines in the text file. This file will be created within the C:\iPC\SavedData folder. The sub-folder "SavedData" is created by the installation program and should not be removed or renamed.

The file will be named with the following format: YYYYMMDD.csv

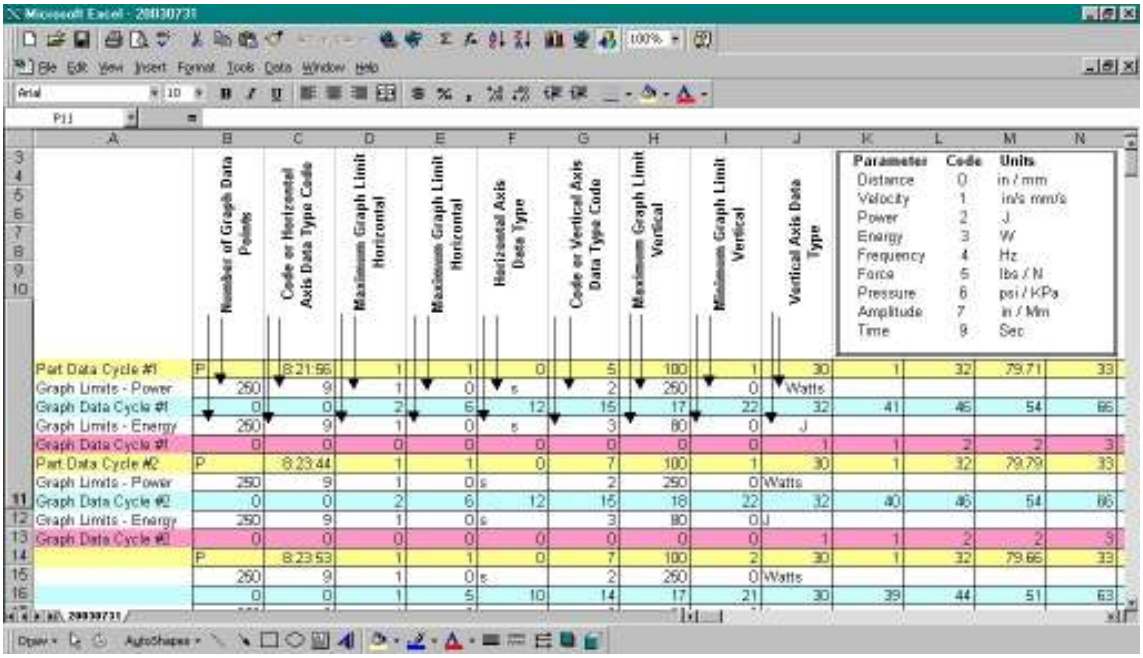
Where YYYY represents the year

MM represents the month (always two digits)

DD represents the day (always two digits)

Note: The example in the diagram on the next page indicates a file for July 31, 2003

Interpreting the Saved Data Format:



If saving graph data is enabled, the iPC software creates each of the following for every part:

1. Characteristic Data.
2. Graph Data for the ‘Left’ graph.
3. Graph Data for the ‘Right’ graph, if this graph was not set to ‘None’.

See descriptions of Part Data and Graph Data below.

The first line, Part Data, includes the values of parameters monitored on the 'Operate' page. To set the list of parameters, the user must set these parameters to 'display' or program a limit window on the 'Process Limits' page.

The application does not write the data on a hard drive immediately. iPC saves all the data in the computers internal buffer. The size of the buffer is 1MB (about 450 parts).

Data will only be saved on a HD (flushed) when:

- There is no room for the next line (the buffer is full), or
- The application is closed, or
- A user disables the feature.

Note: If you want to write saved data on a HD immediately, before the buffer is full or application is closed, you have only to disable and then to enable again the "saving data" checkbox.

Part Data

Interpreting a part data string:

P,HH:MM:SS,XXX,SS,U,N,YZZ,VVVVVVVVVVV[,YZZ,

VVVVVVVVVVV]…….<CR>[<LF>]

Where:

P	The letter "P" is a marker for a new part
HH:MM:SS	Time of the day, in 24-hour format (f. e. 14:00:00 for 2:00 PM)
XXX	Three digit node number
SS	Two digit setup number
U	Units (0 = US, 1 = metric)

N Number of parameters

And for each parameter:

YZZ The parameter's 3-digit code; includes

- Y: Status of the characteristic; status of the part if associated with part count (00): 1 = good, 2 = suspect low, 3 = suspect high, 4 = bad low, 5 = bad high;
- ZZ: the characteristic number (see the ***Characteristics' code numbers and units*** below)

VVVVVVVV The parameter's value
VV

Characteristics' code numbers and units:

Characteristic	**Number**	**Units (US)**	**Units (Metric)**
Parts Counter	00	-	-
Line Pressure	01	psi	kPa
Downstroke Time	10	sec	
Downstroke Distance	11	in	mm
Downstroke Velocity	12	in/s	mm/s
Contact Pressure	13	psi	kPa
Trigger Delay Time	20	sec	
Trigger Delay Distance	21	in	mm
Weld Time P1	30	sec	
Weld Distance P1	31	in	mm
Weld Energy P1	32	j	
Weld Power P1	33	w	
Weld Time P2	40	sec	
Weld Distance P2	41	in	mm
Weld Energy P2	42	j	
Weld Power P2	43	w	
Absolute Weld Distance	50	in	mm
Total Weld Time	51	sec	
Total Weld Distance	52	In	mm
Total Weld Energy	53	j	
Hold Time	60	sec	
Hold Distance	61	in	mm
Total Cycle Time	70	sec	
Total Stroke	71	in	mm

An example string for part data

P,11:46:14,003,01,0,4,100, 24,030, 0.250,032, 0.10,033, 0.2

Means:

Time:	11:46:14 (11 am)
Node ID:	003
Setup number:	01
Units:	0 (US)
Num. Params:	4
Parts Counter:	24 (good part)
Weld Time P1:	0.250 sec
Weld Energy P1:	0.10 j
Weld Power P1:	0.2 w

Graph Data

Interpreting a graph data string:

For every graph crated within iPC, the graph data string will include 1 or 2 sets of graph data:

- Header string has the format:

PPP,H,AAAAAAAAA,BBBBBBBBB,CCCCCCC,V,DDDDDDDDD,EEEEEEEEE,FFFFFFF

Where:

PPP	Number of Data Points
H	Horizontal Data Type (see Parameters' type codes and units below)
AAAAAAAAA	Horizontal Axis Max Value
BBBBBBBBB	Horizontal Axis Min Value
CCCCCCC	Horizontal Units Name (text)
V	Vertical Data Type (see the Parameters' type codes and units below)
DDDDDDDDD	Vertical Axis Max Value
EEEEEEEEE	Vertical Axis Min Value
FFFFFFF	Vertical Units Name (text)

Parameters' type codes and units:

Parameter	Type	Units (US)	Units (metric)
Distance	0	in	mm
Velocity	1	in/s	mm/s
Power	2	J	
Energy	3	W	
Frequency	4	Hz	
Force	5	lbs	N
Pressure	6	psi	KPa
Amplitude	7	in	Mm
Time	9	Sec	

- String with raw data:

NNN,NNN,NNN,NNN,NNN,NNN,NNN,NNN,NNN,NNN,NNN,NNN,NNN,NNN,NNN,NNN,…

This string is omitted if the number of points = 0

Includes up to 250 values, in diapason from 0 to 250, separated with comma. The value 255 stands for missing data point.

For all parameters except Distance:

- For the raw value 0, the real parameter is VertMinValue;

- For the raw value 250, the real parameter is VertMaxValue.

For Distance (Type = 0):

- For the raw value 0, the real parameter is VertMaxValue;

- For the raw value 250, the real parameter is VertMinValue.

How to calculate real data

The horizontal graph value, Hor, for a given horizontal index, I (from 0):

Hor = I * GH + HorzMinValue

where

GH = (HorzMaxValue – HorzMinValue) / 250

Note that 250 is used rather than 255.

The vertical graph value, Ver, for a given horizontal index, I:

a) For parameters other than Distance (Type > 0):

IF DataArray[I] < 255

Ver = (DataArray[I] * GV) + VertMinValue

END

b) For Distance (Type = 0):

IF DataArray[I] < 255

Ver = VertMaxValue - (DataArray[I] * GV)

END

where

GV = (VertMaxValue – VertMinValue) / 250

Note that the value 255 is reserved for missing data points.

When the horizontal axis is any parameter other than TIME, some x, y point values may not be defined.

An example data

250,9,0.500,0.000,s,4,51000,49000,Hz,57,57,57,57,88,88,88,88,156,156,156,156,158,158,158,158,158,…

interpreted as …

Header string:

Number of Data Points:	250
Horizontal Data Type:	9 (Time)
Horizontal Axis Max Value:	0.5 sec
Horizontal Axis Min Value:	0 sec
Horizontal Units Name:	s
Vertical Data Type:	4 (Frequency)
Vertical Axis Max Value:	51000
Vertical Axis Min Value:	49000
Vertical Units Name:	Hz

String with raw data (GH = 0.002; GV = 8):

Point number	i	Raw data	Time (s)	Frequency (Hz)
1	0	57	0.000	49456
2	1	57	0.002	49456
3	2	57	0.004	49456
4	3	57	0.006	49456
5	4	88	0.008	49704
6	5	88	0.010	49704
7	6	88	0.012	49704
8	7	88	0.014	49704
9	8	156	0.016	50248
10	9	156	0.018	50248
11	10	156	0.020	50248
12	11	156	0.022	50248
13	12	158	0.024	50264
14	13	158	0.026	50264
15	14	158	0.028	50264

REFERENCES

Astashev [a], K. and Babitsky[b],V. I. (1998), The Uses of Swept Frequency Microwaves, Ultrasonics - Volume 36, Issues 1-5 , Pages 89-96

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Balamuth, Lewis (1954), Mechanical Impedance Transformers in Relation to Ultrasonic Machining, Research and Development Division, Cavitron Equipment Corporation, Long Island City, New York ,Acoustical Society of America

Chaffin, D.B., Andersson, G.B.J & Martin, B.J. (1999), Occupational Biomechanics. New York, NY: John Wiley & Sons.

Conant, J. (2002), Tuxedo Park. New York, NY: Simon & Schuster.

Cribbs, R. W. (1969), Non-Destructive Testing - Volume 2, Issue 4 , Pages 248-250

Dukane (1995), Guide to Ultrasonic Plastics Assembly. St. Charles, IL: Dukane Corporation.

Dukane (2002), Dynamic Process Controller User's Manual. St. Charles, IL: Dukane Corporation.

Dukane (2005), iPC v1.7 Software Installation Guide. St. Charles, IL: Dukane Corporation.

Esposito, A. (1980), Fluid Power with Applications. Englewood Cliffs, NJ: Prentice-Hall.

Graff, K. F. (1981) A History of Ultrasonics, Chapter 1 of Physical Acoustics, Vol. 15, Mason and Thurston, editors, Academic Press.

Harper, C.A. (1992), Handbook of Plastics, Elastomers and Composites. New York, NY: McGraw-Hill.

Huff, Brian (2002), Enterprise Analysis & Design Class Handout Notes, IDEF3 Process Description Capture Method, UTA, Fall, 2002.

Huff, Brian (2005), Simulation & Optimization Class Handout Notes, UTA, Spring, 2005.

Imrhan, S.N. (2004) Occupational Biomechanics Class Handout Notes, UTA, Summer, 2004.

Lanner Group (1998) Witness© Training Manual General Terminology Version, Version WIN-307, Release 9.00.

Liles, D.H (2004) Topics in Quality Control Continuous Process Improvement Class Handout and Notes, UTA, Fall, 2004.

Masahiko Jin and Masao Murakawa (2001), Journal of Materials Processing Technology - Volume 113, Issues 1-3, Pages 342-347.

Mecasonic SA (1984), Ultrasonic Plastic Welder Standards 84 Technical Booklet, Paris, France.

Popov, E.P. (1976), Mechanics of Materials. Englewood Cliffs, NJ: Prentice-Hall.

Priest, J.W. and Sanchez, J.M. (2001), Product Development and Design for Manufacturing. New York, NY: Marcel Dekker.

Priest, J.W (2005)Technology Development & Deployment Class Handout Notes Metrics for Assessing Technology Deployment, UTA, Summer, 2005.

Priest, J.W (2005)Product Development, Producibility and Reliability Design Class Handout Notes, UTA, Fall, 2005.

Rozenberg, L.D. (1973), Physical Principles of Ultrasonic Technology-Volume 1. New York, NY: Plenum Press.

Rozenberg, L.D. (1973), Physical Principles of Ultrasonic Technology-Volume 2. New York, NY: Plenum Press.

Rozenberg, L.D., Kazantsev, V.F., Makarov, L.O. & Yakhimovich, D.F.(1964), Ultrasonic Cutting. (Authorized translation from the Russian by J.E.S. Bradley, B.Sc.,Ph.D.) New York, NY: Consultants Bureau.

Tsao, C. C. and Hocheng, H. (2004), International Journal of Machine Tools and Manufacture - Volume 44, Issue 10 , August 2004, Pages 1085-1090

United States Pharmacopeia (USP) 28, Physical Tests /

<788> Particulate Matter in Injections, Pages 2448 – 2454.

United States Pharmacopeia (USP) 28, Physical Tests/ <789> Particulate Matter in Ophthalmic Solutions, Pages 2454 – 2455.

Vergara, L., Gosálbez, J., Miralles, R. and Bosch, I. (2004), Ultrasonics - Volume 42, Issues 1-9, Pages 813-818.

Xiao, M., Wang, Q.M., Sato, K., Karube, S., Soutome, T. and Xu, H. (2006), International Journal of Machine Tools and Manufacture - Volume 46, Issue 5, Pages 492-499

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